Examining Multimorbidity in Patients with Psoriasis and the Impact of Biologic Therapies on the Risk of Major Cardiovascular Events

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List of contents

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List of tables

Chapter 2

Chapter 4

Chapter 5

Chapter 6

List of figures

List of abbreviations

AE	Adverse event
AMP	Adenosine monophosphate
BAD	British Association of Dermatologists
BADBIR	British Association of Dermatologists Biologic Interventions Register
BIW	Twice weekly
BMI	Body mass index
BSA	Body surface area
cAMP	Cyclic adenosine monophosphate
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CRP	C-reaction protein
CVD	Cardiovascular disease
CVE	Cardiovascular event
df	Degree of freedom
DIY	Do-it-yourself
DLQI	Dermatology life quality index
DNA	Deoxyribonucleic acid
EGIR	European group for the study of insulin resistance
EMA	European Medicine Agency
EOW	Every other week
FDA	Food and Drug Administration
GWAS	Genome-wide association studies
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
HR	Hazard ratio
ICD	International Classification of Diseases
IDF	International Diabetes Federation
IL	Interleukin
ISRCTN	International Standard Randomised Controlled Trial Number
IV.	Intravenous
MACE	Major adverse cardiovascular event
MedDRA	Medication Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MI	Myocardial infarction
NAFLD	Non-alcoholic fatty liver disease
NBUVB	Narrowed-band ultraviolet B
NCEP: ATP III	National Cholesterol Education Programme: Adult Program Treatment Panel III

NFAT	Nuclear factor of activated T-cell
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
NYHA	New York Heart Association
OR	Odds ratio
ONS	Office of National Statistics
p25	25^{th} percentile
p75	75^{th} percentile
PASI	Psoriasis area and severity index
PDE4	Phosphodiesterase type 4
PGA	Physician global assessment
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PSOR	Psoriasis susceptibility region
PR	Prevalence ratio
PUVA	Psoralen and ultraviolet A
QW	Once weekly
RCT	Randomised controlled trials
RR	Relative risk
SC.	Subcutaneous
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SMD	Standardised mean difference
TG	Triglyceride
Th	T-helper
THIN	The Health Improvement Network
TNF	Tumour necrosis factor
TNFi	Tumour necrosis factor-alpha inhibitor
UVB	Ultraviolet B
UK	United Kingdom
US	United States
VEGF	Vascular endothelial growth factor
WHO	World Health Organisation

Abstract

The University of Manchester

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Doctor of Philosophy

Examining multimorbidity in patients with psoriasis and the impact of biologic therapies on the risk of major cardiovascular events

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Aims: The aims of this thesis were to examine the prevalence of physical and mental health comorbidities in patients with psoriasis and then subsequently examine the impact of biologic therapies on the risk of major cardiovascular events (CVEs) in patients with psoriasis.

Methods: The first aim was achieved by conducting a cross-sectional study of participants enrolled in the UK Biobank. Participants with and without psoriasis were compared in terms of sociodemographic, lifestyle characteristics and the presence of both physical and mental health comorbidities. The prevalence ratios (PRs) with 95% confidence intervals (CIs) were estimated using log-binomial regression models. A multinomial logistic regression model was used to examine differences in the numbers of comorbidities overall, and then separately for both physical and mental health comorbidities for participants with psoriasis compared to those without and findings presented as odds ratios (ORs).

The association between biologic therapies and major CVEs in patients with psoriasis was assessed firstly via a systematic review and meta-analysis of randomised controlled trials (RCTs) and subsequently via a cohort study in the British Association of Dermatologists Biologic Interventions Register (BADBIR). The systematic review and meta-analysis examined the risk of major adverse cardiovascular events [MACEs; myocardial infarction (MI), cerebrovascular accident or cardiovascular death] in adult patients with plaque psoriasis exposed to biologic therapies. Data were obtained from systematic searches in the Cochrane Library, MEDLINE and Embase, the US Food and Drug Administration, the European Medicines Agency, individual pharmaceutical companies online search platforms and five trials registers. RCTs reporting adverse events in adults with plaque psoriasis receiving at least one licensed dose of biologic therapy, conventional systematic therapy or placebo were included. Peto ORs with 95% CIs and I^2 statistics to assess heterogeneity were calculated. The cohort study using data from the BADBIR, compared the risk of major CVEs (acute coronary syndrome, unstable angina, MI or stroke) occurring on therapy or within 90 days after the last dose between different therapies in participants recruited between 09/2007-10/2016. Anti-interleukin-12/23 agent (ustekinumab) was compared with tumour necrosis factor-alpha inhibitors (TNFi; etanercept, and adalimumab) in a main analysis and ustekinumab, etanercept or methotrexate were compared with adalimumab in sensitivity analyses. Overlap weighting by propensity score was used to balance baseline confounders among comparison groups. Cox proportional hazard regression models were used to estimate hazard ratios (HRs) with 95% CIs.

Results: Of the 502,543 participants in the UK Biobank, 6,105 (1.21%) had psoriasis. Patients with psoriasis were associated with an increased prevalence of both physical and mental comorbidities compared with participants without psoriasis. Participants with psoriasis were significantly more likely to report cardiovascular risk factors, including hypertension [PR adjusted for age, sex and socioeconomic deprivation: 1.13 (95% CI 1.09 – 1.17)], high cholesterol [adjusted PR: 1.10 (95% CI 1.03 – 1.17)] and diabetes [adjusted PR: 1.26 (95% CI 1.15 – 1.38)]. The prevalence rates of inflammatory arthritis (psoriatic arthritis or rheumatoid arthritis) showed the largest difference between the psoriasis group and the no psoriasis group (16.9% vs 1.1%). Patients with psoriasis were also more likely to smoke and not engage in regular physical activity. The overall numbers of comorbidities, and also when considered separately for physical and mental disorders, were higher for patients with psoriasis.

Overall, 38 RCTs involving 18,024 patients with plaque psoriasis were included in the systematic review and meta-analysis. No MACEs were observed in 29 studies, while nine RCTs reported 10 patients experiencing MACEs. There was no statistically significant difference in the risk of MACEs associated with the use of biologic therapies overall [OR 1.45 (95% CI 0.34 – 6.24); TNFi (adalimumab, etanercept and infliximab) [OR 0.67 (95% CI 0.10 - 4.63)]; anti-IL-17A agents (secukinumab and ixekizumab) [OR 1.00 (95% CI 0.09 - 11.09)] or ustekinumab [OR 4.48 (95% CI 0.24 – 84.77)]. No heterogeneity was observed in these comparisons.

5,468 biologic-naïve patients with plaque psoriasis subsequently exposed (951 ustekinumab; 1,313 etanercept; and 3,204 adalimumab) from the BADBIR were included in the main analysis of the cohort study. Secondary analyses also included 2,189 patients receiving methotrexate. No differences in the risk of major CVEs were observed between biologic therapies [adjusted HR for ustekinumab vs TNFi (etanercept or adalimumab): 0.98 (95% CI 0.43 – 2.25); ustekinumab vs adalimumab: 0.87 (95% CI 0.33 – 2.30); etanercept vs adalimumab: 0.82 (95% CI 0.28 – 2.36); methotrexate vs adalimumab: 1.06 (95% CI 0.34 – 3.28)]. Overall, there were no significant differences in the risk of major CVEs between three different biologic therapies and methotrexate.

Conclusions: Psoriasis is associated with a number of mental health and physical comorbidities including cardiovascular risk factors. Patients with psoriasis were more likely to have deleterious lifestyle habits such as smoking and not undertaking regular physical activity. The findings presented in the meta-analysis suggest that there was no significant difference in the risk of MACEs in psoriasis patients treated with biologic therapies compared with placebo or the different doses of the same biologic therapies. Moreover, no significant difference in the risk of major CVEs was observed in patients treated with biologic therapies compared with different biologic therapies or methotrexate in the cohort study using the BADBIR. The findings suggest that the risk of major CVEs should not be a key discriminator for selecting specific biologic therapies for psoriasis patients. Future larger, well-designed cohort studies with longer follow-up are needed to examine the longer-term impact of biologic therapies on the risk of major CVEs.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning

Copyright statement

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Preface

Watcharee Rungapiromnan graduated from Chulalongkorn University, Thailand with a Bachelor's degree in pharmaceutical science in 2005. She worked at two private hospitals as a hospital pharmacist for two years. She then subsequently worked at the National Health Product Vigilance Centre at the Thai Food and Drug Administration (FDA). Her early experience involved clinical practice and pharmacovigilance. In 2009, she was awarded a scholarship by the Royal Thai Government to undertake a Master's degree. She graduated from the University of Hertfordshire in the UK, with a Master's degree with commendation in Advancing Pharmacy Practice in 2010. After the graduation, she continued her post at the Thai FDA for four years. Her responsibilities sparked her interest in pharmacoepidemiology since several risk minimisation tools launched by the Thai FDA were developed owing to findings from pharmacoepidemiology studies. She was awarded a PhD scholarship by the Royal Thai Government to study Pharmacy and Pharmaceutical Sciences. She started her PhD programme at the Centre for Pharmacoepidemiology and Drug Safety, Division of Pharmacy and Optometry, Faculty of Biology, Medicine and Health, the University of Manchester in 2014. Her research focused on examining multimorbidity in patients with psoriasis and the impact of biologic therapies on the risk of major cardiovascular events.

List of publications arising from this work

Published papers:

1. Rungapiromnan W, Yiu ZZN, Warren RB, Griffiths CEM, Ashcroft DM. Impact of biologic therapies on risk of major adverse cardiovascular events in patients with psoriasis: systematic review and meta-analysis of randomized controlled trials. British Journal of Dermatology. 2017;176(4):890-901.

2. Rungapiromnan W, Yiu ZZN, Warren RB, Griffiths CEM, Ashcroft DM. Reply to 'Impact of biologic therapies on risk of major adverse cardiovascular events in patients with psoriasis: systematic review and meta-analysis of randomized controlled trials': reply from the authors. British Journal of Dermatology. 2017;177(6):1766-67.

Submitted paper:

1. Rungapiromnan W, Mason KJ, Lunt M, McElhone K**,** Burden AD**,** Rutter MK, Warren RB, Griffiths CEM, Ashcroft D.M., BADBIR Study Group. Risk of major cardiovascular events in patients with psoriasis receiving biologic therapies: prospective cohort study.

Publications from conference presentations:

1. Rungapiromnan W, Mason KJ, Lunt M, McElhone MK, Rutter MK, Warren RB, Griffiths CEM, Ashcroft DM and BADBIR Study Group. Risk of major cardiovascular events in adult patients with psoriasis treated with biologic therapies or methotrexate: cohort study in the British Association of Dermatologists Biologic Interventions Register (BADBIR). Pharmacoepidemiology and Drug Safety 2018;27(Suppl.2):467 (Accepted for a poster presentation at the *3*4th International Conference on Pharmacoepidemiology and Therapeutic Risk Management in Prague, Czech Republic during 22nd – 26th August 2018)

2. Rungapiromnan W, Mason KJ, Lunt M, McElhone K, Rutter MK, Warren RB, Griffiths CEM, Ashcroft DM, BADBIR Study Group. Association between biologics and major cardiovascular events in adult patients with plaque psoriasis: a cohort study in the British Association of Dermatologists Biologic Interventions Register (BADBIR). Journal of Investigative Dermatolgy 2018;138(5)(Suppl):S87. (Accepted for an oral presentation at the International Investigative Dermatology Meeting in Florida, the United States during 16th – 19th May 2018)

3. Rungapiromnan W, Warren RB, Yiu ZZN, Griffiths CEM, Ashcroft DM. Risk of major adverse cardiovascular events associated with biologic therapies in patients with plaque psoriasis: systematic review and meta-analysis of randomised controlled trials. Pharmacoepidemiology and Drug Safety 2016;25(Suppl.3):536-7. (Accepted for a poster presentation at the 32nd International Conference on Pharmacoepidemiology and Therapeutic Risk Management in Dublin, Ireland during 25th – 28th August 2016)

4. Rungapiromnan W, Warren R, Yiu Z, Griffiths CEM, Ashcroft DM. Impact of biological therapies on risk of major adverse cardiac events in patients with psoriasis: a meta-analysis of randomized controlled trials. British Journal of Dermatology 2016;175(Suppl.S1):42. (Accepted for a poster presentation at the 96th Annual Meeting of the British Association of Dermatologists in Birmingham, the UK during 5th – 7th July 2016)

Academic achievements

Fundamentals of epidemiology (My grade was 90%)
Advanced epidemiology (My grade was 70%)
Statistics modelling in STATA (My grade was 84%)

Chapter 1

Overview of thesis structure

1.1 Introduction

Psoriasis is a common, incurable chronic inflammatory skin disease that has a major impact on patients' quality of life.[1] Estimates suggest that over 125 million people have psoriasis worldwide.[2,3] In the UK, recent estimates indicate that almost 3% of the population have psoriasis.[4] In 2014, the World Health Organisation (WHO) recognised psoriasis as a global concern; highlighting the impact of the condition and the burden of comorbidities.[1]

Existing evidence suggests that patients with psoriasis are at high risk of a number of comorbidities.[5] However, the prevalence and the associations of these comorbidities with psoriasis are not well established with wide ranges reported in previous studies. Furthermore, the nature and extent of comorbidities related to psoriasis, and how lifestyle factors may play a role in these relationships is essential to understand in detail. To study this question robustly requires large population databases designed to capture the comorbidities and lifestyle of patients with psoriasis. The UK Biobank is a large population database of about 500,000 participants.[6] It has prospectively collected clinical and lifestyle information among participants in the UK. It is an invaluable source to explore these knowledge gaps.

Over the last decade, biologic therapies have had an increasing role in the treatment of psoriasis. However, the cardiovascular safety profile of these therapies is still unclear. Existing studies have suggested both potential positive and negative effects of different biologic treatments on cardiovascular disease (CVD) among patients with psoriasis. The number of studies examining this association is limited and their study designs are often biased due to the selection of comparator treatments. Although several biologic therapies for the treatment of moderate-severe psoriasis have been approved for over 10 years, there has been no systematic review and meta-analysis examining the impact of all licensed biologic therapies on the risk of major adverse cardiovascular events (MACEs) in patients with psoriasis. To understand this association, a systematic review and meta-analysis of randomised controlled trials (RCTs), a top hierarchy of evidence-based practice, is needed.

Patients with psoriasis in real-life practice tend to have different characteristics from those seen in RCTs such as having more comorbidities are often use treatments for much longer periods that examined within the trials. Prospective cohort studies can take into account these limitations of RCT. Thus, this study design is required to evaluate the association between biologic therapies and cardiovascular events (CVEs) in patients with psoriasis in real-life practice. There were cohort studies examining the association between biologic therapies and CVEs but they had some limitations such as using inappropriate reference groups and insufficiently controlling for cardiovascular confounders.[7–11] Therefore, it requires well-designed prospective cohort studies to evaluate the association between major CVEs and biologic therapies among patients with psoriasis. The British Association of Dermatologists Biologic Interventions Register (BADBIR) is a prospective cohort study which has collected detailed information from patients with psoriasis treated with biologic therapies or conventional systemic

therapies across the UK and Republic of Ireland.[12] Detailed information is collected routinely on exposure to treatments, the severity of psoriasis and comorbidities. Thus, it is an invaluable source for examining this association.

In summary, given the gaps in the existing knowledge, this thesis aimed to examine the prevalence of comorbidities in patients with and without psoriasis using the UK Biobank database. Moreover, the association between biologic therapies and CVEs in patients with psoriasis was assessed using a systematic review and meta-analysis of RCTs and a prospective cohort study in the BADBIR.

1.2 Thesis structure

The chapters of this thesis are outlined as follows.

Chapter 1: Overview of thesis structure

Chapter 2: Psoriasis: epidemiology and management

This chapter covers information on psoriasis epidemiology, aetiology, types and severity of psoriasis, comorbidities, the treatments of psoriasis and the economic impact of psoriasis. In addition, the relationship between biologic therapies and CVD; and rationale for this thesis are presented.

Chapter 3: Aims and objectives

Chapter 4: Examining the demographic and anthropometric characteristics of patients with psoriasis and prevalence of physical and mental health comorbidities: cross-sectional study of the UK Biobank

This chapter describes the baseline characteristics of participants with and without psoriasis. Moreover, it presents the prevalence rates of comorbidities among participants with and without psoriasis; and prevalence ratios using the data from the UK Biobank database.

Chapter 5: **Examining the association between major adverse cardiovascular events and biologic therapies in adult patients with psoriasis: systematic review and meta-analysis**

This chapter presents the results of a systematic review and meta-analysis of RCTs to examine the risk of MACEs in adult patients with plaque psoriasis that are exposed to biologic therapies.

Chapter 6: Risk of major cardiovascular events in patients with psoriasis receiving biologic therapies: prospective cohort study

This chapter presents the findings from a prospective cohort study conducted in the BADBIR examining the risk of major CVEs associated with biologic therapies.

Chapter 7: Discussion

This chapter summarises the key findings of this thesis, discusses their contribution to the current literature, and reflects on the strengths and limitations of the research studies presented in this thesis. Moreover, the implications for clinical practice and policy based on the findings; and recommendations for future research are described.

Chapter 2

Psoriasis: epidemiology and management

2.1 Introduction

Psoriasis is one of the most common immune-mediated inflammatory skin diseases.[13] It has a profound impact on patients' physical, psychological and social life.[14,15] The WHO recently recognised psoriasis as a chronic non-communicable painful, disfiguring and disabling disease and encouraged member states to raise awareness and care for patients with psoriasis.[16] The WHO also acknowledged that psoriasis patients were at an increased risk of CVD, diabetes mellitus, heart attack, stroke, metabolic syndrome, Crohn's disease, ulcerative colitis and liver disease. Psoriasis can have a major burden on healthcare systems and society more broadly due to the costs of treatments of psoriasis and other comorbidities; and loss of productivity of patients, their families and caregivers.[17]

The aim of this chapter is to provide an overview of psoriasis, its comorbidities, treatment and economic impact. Finally, a rationale for this thesis will be described.

2.2 Epidemiology

One hundred and twenty-five million people (2% or 3% of the world population) suffer from psoriasis worldwide.[2] In the UK, approximately 1.8 million people suffer from this disease.[18] However, estimates of the prevalence of psoriasis vary considerably between different countries.[19] Parisi et al. (2013) conducted a systematic review examining the prevalence and incidence of psoriasis in the general population and assessed 46 and seven articles, respectively.[19] The variation in psoriasis prevalence and incidence was associated with age and geographic region. However, there was no evidence to suggest that gender had an influence on the prevalence or incidence of psoriasis.[19] In adults, the prevalence varied from 0.91% (the US) to 8.5% (Norway). The UK prevalence rate ranged from 1.3 – 2.6%. The prevalence rates from countries which were closer to the equator (Latin America, Tanzania, Egypt, India, Sri Lanka, China and Taiwan) were lower (< 0.5%). In children, the prevalence varied between different studies from 0% (Taiwan) – 2.1% (Italy). The US incidence rate in all age groups, based on the Rochester Epidemiology Project, was 59.9 per 100,000 person-years. This incidence rate increased with age up to 39 years of age and declined thereafter and reached a peak again in people aged 50-69 years. In the systematic review, estimates of incidence of psoriasis in adults varied from 78.9 per 100,000 person-years (the US) to 230 per 100,000 person-years (Italy). In children, the US incidence rate was approximated as 40.8 per 100,000 person-years. Comparisons of prevalence and incidence between countries or regions may be difficult due to differences in study designs/methodologies (e.g. physician's or self-reported diagnoses, definitions of psoriasis, types of databases used, methods of data collection, and sampling techniques) and patients' characteristics (e.g. genetic factors) and other factors (e.g. environmental factors and healthcare systems). All of these factors can have an influence on the results of studies examining prevalence and incidence of psoriasis.

There are suggestions that the prevalence of psoriasis is increasing. This upward trend of psoriasis was observed in several countries e.g. from 2.3% in 1999 to 2.8% in 2013 in the UK[4], from 4.8% during 1979-1980 to 11.4% during 2007-2008 in Norway[3,20], from 1.43% in 1998 to 2.31% in 2013 in Spain[20,21]. The reasons for the rising trends may be due to changes in lifestyle and environmental factors, increased awareness about psoriasis, and improvements in life expectancy.[3,4]

2.3 Economic impact of psoriasis

Psoriasis not only impairs patients' quality of life but also poses a financial burden for healthcare providers and patients.[1,17]

Total costs for psoriasis treatment can vary between countries owing to the different severity of psoriasis, treatments available, prices of treatments, healthcare services, healthcare facilities and systems used.[17] An Italian study which was conducted before the initiation of biologic therapies for psoriasis collected data on direct medical and indirect costs (loss of productivity) from six dermatology departments for 1 year during 2003-2004. It found that the mean cost for psoriasis treatment was about 5,226 euros/year for patients with moderate psoriasis [Psoriasis Area and Severity Index (PASI) ≤ 20] while patients with more severe psoriasis (PASI > 20) had the higher mean cost of 11,434 euros/year. However, these calculations did not include some costs such as patient out-of-pocket expenses.[22]

The cost of biologic therapies for the treatment of psoriasis is much more expensive than that of conventional systemic therapies.[23] This cost also has an effect on the total cost of psoriasis treatment as a whole. A UK study examined costs and clinical outcomes of psoriasis treatment before and after the start of biologic therapies for patients with moderate-severe plaque psoriasis.[23] The data were collected from a specialist psoriasis clinic in a hospital in London and the total healthcare costs regarding the treatment of psoriasis in the biologic therapies group (£11,981 /patient/year) were significantly higher than that of conventional systemic therapies group (£4,207 /patient/year). In terms of clinical outcomes, the number and length of hospital admission in the biologic therapies group were significantly decreased when compared with the conventional systemic therapies group.[23] Nonetheless, the estimated costs in this study were still underestimated since some non-healthcare costs (e.g. loss of productivity) were not included.

Since psoriasis and its associated comorbidities can interfere with patients' daily activities, ability to work and employment prospects then this may also impact on personal income and/or future earnings.[24] Some patients with psoriatic arthritis may also be unable to work due to this condition.[24] In addition, the average sickness absence among workers with psoriasis corresponds to the severity of psoriasis: 14 days/year for moderate-severe psoriasis[25] and up to 26 days/year for severe psoriasis[26]. In the UK, figures are higher than the average rate of sickness absence rate (4.3 days/year).[26] Moreover, the level of work impairment and the

possibility of being unemployed also increase with the severity of psoriasis.[27,28] It is estimated that the cost of psoriasis relating to presenteeism and sickness absence is approximately £1.07 billion/year in the UK[28]

2.4 Aetiology

Although the exact mechanisms that cause psoriasis are unclear, it is clear that genetic, immunologic and environmental factors play a role in the aetiology of the condition.[29] In most cases, multiple genes predispose people to psoriasis. Up to 70% of patients with psoriasis have a family member with the disease. The major genetic determinant of psoriasis is in the major histocompatibility complex (MHC) region. MHC is the area for genes which encode human leucocyte antigen (HLA).[30] There are 41 genome-wide susceptibility loci associated with psoriasis including the HLA region on chromosome 6.[31] This locus is defined as the psoriasis susceptibility region 1 (PSOR1)[32–35] and accounts for 30-50% of the heritability of psoriasis. Other relevant genetic loci have been identified through genetic specific and genome-wide association studies (GWAS).[36,37] PSOR1 lies in HLA-Cw*06 which has a strong association with psoriasis.[38,39] HLA-Cw*0602 is a major genetic determinant of psoriasis vulgaris which is the commonest type and it also has a strong association with guttate psoriasis.[40]

The immunopathogenesis of psoriasis involves innate and adaptive immune systems. They lead to alterations in skin and vasculatures.[41] T-helper (Th) 17 and Th1 cells play an important role in the pathology of psoriasis. These cells are differentiated from naïve T-cells in the skin due to elevated production of dendritic antigen-presenting cells. This differentiation induces an immune response characterised by secretion of certain cytokines such as tumour necrosis factor (TNF)-alpha, interleukin (IL)-12, IL-23, IL-17 and interferon-gamma. Upregulation of these cytokines results in skin hyperproliferation and inflammation. This process leads to cells being forced to the skin surface and accumulating. It represents dead scales which are characteristic of the psoriasis plaque.[41,42] Chronic stimulation of these pathways leads to epidermal thickening and erythema due to an increased blood flow to the skin through angiogenesis and vasodilation.[43] Better understanding in the pathogenesis of psoriasis has led to the development of more selective biologic therapies.[44]

In addition, the environmental factors are also able to trigger psoriasis in predisposed individuals. These factors include infections (e.g. streptococcal infections); certain medicines (e.g. lithium, beta-blockers, non-steroidal anti-inflammatory drugs and tetracyclines); rapid systemic corticosteroid withdrawal; excess alcohol consumption; smoking (strongly associated with palmoplantar pustulosis); stress (is related to onset and severity of psoriasis); and ‘Koebner phenomenon’ (is new plaques of psoriasis which appear at skin trauma sites).[38,39]

2.5 Types of psoriasis

Psoriasis is a chronic inflammatory skin disease[13] and usually follows relapsing and remitting courses.[39] Psoriasis can occur in any sex, race, age but most cases occur before 35 years of age.[45] It peaks at ages 16-22 years and 55-60 years. At the first peak, it is commonly associated with a family history of psoriasis.[39]

Psoriasis is divided into four distinctive presentations:

1. Psoriasis vulgaris or chronic plaque psoriasis

This is the commonest type (90% of patients with psoriasis).[45,46] Papulosquamous plaques are well-delineated from the surrounding area. The plaques are pinkish or red and covered by white or silver scales. They may be thick, thin, large or small. At the edges, the plaques are most active. The lesions may be annular with normal skin at the centre. The plaques are usually distributed symmetrically and typically occur on extensor surfaces of the knees, elbows, low back, post-auricular, scalp, lumbosacral region and umbilicus. New plaques of psoriasis develop at sites of skin trauma – so-called Koebner phenomenon.[13,39,47]

2. Flexural or inverse psoriasis

Flexural psoriasis is characterized by well-demarcated, red shiny plaques confined to flexures e.g. groin, natal cleft, and submammary areas. It is typically devoid of scale. Secondary infections especially *Candida* infection are common.[13,38,39]

3. Guttate psoriasis

This type tends to occur in children and adolescents. It is an acute form of psoriasis. Papules which are less than one centimetre in diameter erupt on the trunk often about two weeks after beta-haemolytic streptococcal infections.[13]

4. Generalised pustular psoriasis (Von Zumbushch psoriasis)

This is an acute and severe form of psoriasis. Moreover, it can be life-threatening. Small, monomorphic sterile pustules arise in areas of painful inflamed skin over the trunk and extremities. Typically, these pustules will become dry and peel. In some patients, the pustules may form large “lakes of pus”. Pustules can also present in the oral cavity (geographic tongue). Patients with this type usually develop systemic symptoms including fever, chills, diarrhoea and arthralgia. Abrupt withdrawal of systemic and sometimes ultra-potent topical corticosteroids may trigger this condition.[13,48]

Associated features

Nails

Up to 50% of psoriasis patients experience nail changes. Nail changes consist of five types: 1) pitting of the nail plate (the commonest); 2) nail plate separation (onycholysis); 3) oil spots (yellow-brown subungual discolouration); 4) subungual hyperkeratosis; and 5) rarely a

damaged nail matrix and lost nail plate. Most patients with psoriatic arthritis experience nail changes.[13,39]

Scalp

At least 50% of patients have scalp psoriasis. Plaques usually form on the scalp and around the hair margin. The extent of psoriasis can be very mild (slight and fine scaling) to very severe (thick and crusted plaques which cover the whole scalp). Moreover, scalp psoriasis can expand to the forehead, the back of the neck and the ears. When psoriasis presents only on the scalp, it may look similar to other skin diseases such as seborrheic dermatitis. Seborrheic dermatitis looks yellowish and greasy while scalp psoriasis looks powdery with a silvery sheen.[49]

2.6 Severity of psoriasis

Measures of disease severity are used to evaluate the extent of psoriasis, the impact on patient's quality of life and/or responsiveness to the treatment. It is estimated that approximately 80% of patients have mild to moderate plaque psoriasis whereas 20% of them have moderate to severe disease.[29,50] However, at present, there is no international standard or validated categories for the severity of psoriasis.[51,52] As the ultimate goal of psoriasis treatment is to improve patient's quality of life[53], assessment of psoriasis considers two main aspects; namely, the clinical manifestations and impact on quality of life. Examples of tools commonly used for measuring the clinical manifestation include the PASI and the Body Surface Area affected (BSA). The PASI is the most commonly used rating scale and assesses area coverage and plaque appearance. It examines the degree of erythema, induration/thickness and scaling of plaques over four areas: head, trunk, upper and lower limbs.[54] However, this tool has some limitations. For instance, it is a very complicated tool and not sensitive to change when plaque involvement is limited.[54] The BSA measurements involve determining how much psoriasis lesions involve the body surface area. The hand is estimated to equal to 1% of body surface area.[55] This tool is easy to use but it can result in a 50% overestimation of BSA involvement.[54] The Dermatology Life Quality Index (DLQI) is the most widely used tool for assessing quality of life.[54] It includes 10 questions examining how much patients' skin problems have an effect on their life. This tool has some limitations such as not fully capturing emotions and mental health, and not being very sensitive to small impairments.[54]

The National Psoriasis Foundation defines mild, moderate and severe psoriasis as BSA < 3%, 3 - 10% and > 10% respectively.[2] According to European consensus[56], the severity of psoriasis is categorised into only two severities grades which are mild and moderate-severe psoriasis. Both BSA and PASI are used for the measurement of severity of plaque psoriasis. Mild psoriasis is defined as BSA ≤ 10% and PASI ≤ 10 and DLQI ≤ 10, and moderate-severe psoriasis is defined as BSA >10% or PASI > 10 and DLQI > 10. The National Institute for Health and Care Excellence (NICE) defines severe psoriasis as either treated with phototherapy or systemic therapies, or requiring hospital admissions (outpatient visits) due to psoriasis and psoriatic arthritis and very severe psoriasis is defined as psoriasis patients having PASI ≥ 20

and DLQI >18.[45] The Scottish Intercollegiate Guidelines Network (SIGN) categorises psoriasis severity into two types for the purpose of referrals and selection of treatment.[51] It defines mild psoriasis as DLQI ≤ 5 and psoriasis patients with this type tend to be managed in primary care. For severe psoriasis, it is defined as requiring systemic or biologic therapy. This type is defined as PASI ≥ 10 and DLQI ≥ 10. The SIGN does not provide an operational definition for moderate psoriasis in their guidelines.

It can be seen that major health policy organisations define psoriasis severity differently and the tools for measuring the severity of psoriasis have varying limitations. With these differences, interpretation of the results of meta-analysis or review articles or comparison of the results of studies should be considered carefully taking account of the definition of psoriasis severity referred to in the studies.

2.7 Comorbidities

Emerging epidemiological evidence suggests that psoriasis is associated with an increased risk of a number of comorbidities which include both mental and physical conditions such as psychosocial disorders, psoriatic arthritis, Crohn's disease, hypertension, dyslipidaemia, obesity, diabetes, and CVD. Psoriasis disease severity appears to influence the development of these comorbidities.[57] These comorbidities can increase the complexity of psoriasis management and tend to increase with age.[58] Recognition of comorbidities is essential for providing comprehensive healthcare services, choosing appropriate treatments and monitoring for patients with psoriasis. This section will provide an overview of the most common comorbidities occurring in patients with psoriasis.

2.7.1 Psychosocial comorbidities

Psoriasis has a major negative impact on patients' quality of life[1] and this is related to a variety of psychological problems such as poor self-esteem, anxiety, depression and suicidal ideation. These psychological problems have an effect on patients' activities of daily life (e.g. the selection of clothing and playing sports) and social relations. Misunderstandings in the general population about psoriasis can also have an adverse effect on patients with psoriasis. For example, perceptions that psoriasis is a contagious disease can cause exclusion of psoriasis patients from engaging in routine activities. This can also lead to psychological problems such as low self-esteem.[1]

Psychological comorbidities are prevalent in patients with psoriasis. They were reported to be as high as 67% of 2,391 patients with psoriasis vulgaris in an Italian study.[59] Several studies have found that patients with psoriasis feel self-conscious, disturbed or inconvenienced by the appearance of the affected skin, often avoiding social interaction.[60,61] The results of the Italian study mentioned above also showed that psoriasis affected patients' social functioning and decreased efficiency at work in more than 50% of the patients.[59] The results of a review of

published articles during 1986 - 2009 showed that psoriasis had a negative impact on many aspects of quality of life such as stigmatisation, embarrassment, and social inhibition and found that younger patients with psoriasis were more likely to have more strong feeling of stigmatisation than patients with a similar clinical picture later in life.[61]

A population-based cohort study conducted using a US database which compared incidence rates of psychiatric disorders between a cohort of paediatric psoriasis patients (n=7,404) and psoriasis-free control children (n=37,202) found that psoriatic patients had higher prevalence rates of developing psychiatric disorders (5.13% in the psoriasis group vs 4.07% in the control group), particularly depression (3.01% in the psoriasis group vs 2.42% in the control group), and anxiety (1.81% in the psoriasis group vs 1.35% in the control group).[62] Psychiatric disorders have been found to be more common in female patients.[63,64] In addition, studies have reported that patients with extensive psoriatic disease reported higher rates of depression and suicidal ideation than patients with milder psoriasis.[65,66]

There have been a number of studies examining the association between psoriasis and psychological comorbidities. However, the prevalence rates of these comorbidities vary widely as reported in the above studies. The causes of this difference may be due to different study designs, definitions of outcomes and methods measuring psychological problems in patients with psoriasis. Some studies used interviews, questionnaires, and diagnosis codes to identify the outcomes of the studies.[59,62]

2.7.2 Psoriatic arthritis

Psoriatic arthritis, a debilitating seronegative spondyloarthropathy, is commonly associated with psoriasis with prevalence rates ranging from 7 - 42%.[67] However, most experienced clinicians estimate that the rate is 25%.[68–71] Up to 20% of patients with psoriatic arthritis present with joint disease prior to skin involvement.[72] Even though the rates of psoriatic arthritis are more likely to correlate with the severity of psoriasis: 6% of patients with minimal psoriasis have psoriatic arthritis while 56% of patients with BSA > 10% experience psoriatic arthritis,[68,73] the extent of skin disease shows that it is not related to the severity of joint disease.[74] An increased likelihood of experiencing psoriatic arthritis can be predicted by presenting nail dystrophy, scalp lesions, and intergluteal or perianal psoriatic lesions.[69] Nail lesions, in particular, are more common among patients with psoriatic arthritis compared to patients with psoriasis alone or rheumatoid arthritis.[75]

Psoriatic arthritis most commonly presents as an asymmetric oligoarthritis or polyarthritis with pain and stiffness.[76] Psoriatic arthritis can affect the peripheral joints, axial skeleton, entheses as well as tenosynovial sheaths. However, mostly it affects the joints of the hands, wrists, feet ankles, knees and shoulders.[77] Within the first year of disease onset, 40-60% of patients develop joint damage.[78–80]

The accurate diagnosis of psoriatic arthritis is a problem for epidemiologic studies examining the prevalence of psoriatic arthritis and the association between psoriasis and psoriatic arthritis since there are no validated diagnostic criteria.[81] Moreover, the spectrum of manifestation of psoriatic arthritis is large. It tends to be relapsing and remitting. Therefore, it is not easy to distinguish psoriatic arthritis from rheumatoid arthritis and other arthropathies.[81] Therefore, misdiagnosis of psoriatic arthritis could happen. This is one source of bias of studies relating to psoriatic arthritis.

A recent systematic review and meta-analysis of case-control, cross-sectional and cohort studies examined the association between psoriatic arthritis and CVD.[82] It compared patients with psoriatic arthritis and the general population. The results of the study showed that psoriatic arthritis was significantly associated with the risk of CVD [defined as angina, ischemic heart disease, coronary artery disease, myocardial infarction (MI), or a combination of these outcomes] with odds ratio (OR) 1.43 [95% confidence interval (CI) 1.24 – 1.66], incident CVEs (only cohort studies included) with OR 1.55 (95% CI 1.22 -1.96), MI with OR 1.68 (95% CI 1.31–2.15), cerebrovascular diseases (defined as stroke or transient ischaemic attack) with OR 1.22 (95% CI 1.05–1.41) and heart failure with OR 1.31 (95% CI 1.11–1.55). The association between psoriatic arthritis and CVD may be related to an increased arterial stiffness which is a cardiovascular risk factor.[83] This increase may accelerate the atherosclerosis process in patients with psoriatic arthritis.

2.7.3 Non-alcoholic fatty liver

Patients with psoriasis have an increased risk of liver disease as a complication of high levels of alcohol consumption and use of anti-psoriatic treatments such as methotrexate. However, there is emerging evidence that psoriasis is independently related to non-alcoholic fatty liver disease (NAFLD).[84] NAFLD involves a wide range of liver diseases such as hepatic steatosis, steatohepatitis and hepatic cirrhosis (not related to alcohol intake) and is now considered as the hepatitis manifestation of the metabolic syndrome.[85] It has been suggested that NAFLD leads to endothelial dysfunction that can result in developing CVD.[86]

In the general population, the prevalence of NAFLD has been estimated to be 20-30% in developed countries.[85] There are two small studies examining the prevalence rate of NAFLD in patients with psoriasis. One study found that patients with psoriasis had a prevalence rate of NAFLD of 47% (n=61) compared with 28% in the control group.[87] The severity of psoriasis was higher in psoriasis patients with NAFLD in comparison to patients without NAFLD. Another study conducted in Italy reported that the prevalence of NAFLD in patients with psoriasis was 59.2% (n=84).[88] This study compared psoriatic patients with non-psoriatic patients undergoing biopsy to detect NAFLD. The results of this study confirmed that patients with psoriasis were more likely to have severe liver disease than non-psoriatic patients.

Inflammation plays a crucial role in the pathogenesis of NAFLD. Gisondi et.al suggested that the inflammatory mediators increased in psoriasis can result in the development of insulin resistance and progression to NAFLD.[87] Given this, it has also been suggested that inflammation related to NAFLD precipitates a more severe form of psoriasis.[87,89]

2.7.4 Inflammatory bowel disease

Inflammatory bowel disease (Crohn's disease and ulcerative colitis) are common relapsing immune-mediated inflammatory disorders of the gastrointestinal tract. The pathogenesis of Crohn's disease and psoriasis involve IL-4, IL-13 and IL-23 which are key cytokines for both diseases. The prevalence of Crohn's disease is approximately 0.007% in the general population in the US.[90] Crohn's disease is more likely to occur in psoriatic patients in comparison to controls.[91–93] Several case-control studies have reported that 7-11% of patients with Crohn's disease also have psoriasis.[92–94] A case-control study conducted in Israel using a population-based database included 12,502 psoriasis patients and 24,287 controls. The results showed that the prevalence of ulcerative colitis in psoriasis patients (0.5%) was significantly higher than that of controls (0.3%) ($p = 0.001$).[95]

In another population-based study, patients with Crohn's disease and ulcerative colitis were more like to develop arthritis, psoriasis and asthma compared with controls.[96] Since several genetic susceptibility loci are common to Crohn's disease and psoriasis, patients with psoriasis have a higher likelihood of developing Crohn's disease.[97,98] The association between psoriasis and inflammatory bowel disease is compelling and suggests that they share similar genetic factors and potentially overlapping pathogenesis.[84]

2.7.5 Cancer

The relationship between psoriasis and cancer has been suggested in a number of studies, but there remains uncertainty in relation to particular cancer types. This relationship is more difficult to assess due to the additional effect of phototherapy and immunosuppressive treatment which may increase malignancy risk. [84]

A systematic review and meta-analysis of 37 studies examining the association between cancer risk and psoriasis was published in 2013 which compared the risk of cancer between psoriatic patients and the general population.[99] The results suggested that psoriasis was associated with an increased risk of some solid cancers (respiratory tract, upper aerodigestive tract and liver). Moreover, psoriasis was associated with an increased risk of non-Hodgkin lymphoma, squamous cell carcinoma, and basal cell carcinoma. However, the results suggested that psoriasis might not be associated with an elevated risk of melanoma

Current evidence seems to suggest that psoriasis is associated with an increased risk of specific cancers, but further well-designed studies controlling for important confounders (such

as smoking, alcohol consumption and psoriasis treatment) are required to fully elucidate this association.[84]

2.7.6 Cardiovascular risk factors

2.7.6.1 Hypertension

Hypertension is an important cardiovascular risk factor associated with an increased risk of cardiovascular morbidity and mortality.[84] The association between hypertension and psoriasis corresponds to the severity of psoriasis.[100] Hypertension is more prevalent in patients with psoriasis than patients without psoriasis and the prevalence increases with the severity of psoriasis.[100] The prevalence rates of hypertension reported ranged widely from 8.9 – 44.4% for unspecified severity of psoriasis, 15.1 – 32% for mild psoriasis and 19 – 40.3% for moderate-severe psoriasis.[101–105]

A meta-analysis of 24 observational studies reported an increased prevalence of hypertension among patients with psoriasis with ORs of 1.58 (95% CI 1.42 – 1.76) for psoriasis, 1.30 (95% CI 1.15 – 1.47) for mild psoriasis and 1.49 (95% CI 1.20 – 1.86) for severe psoriasis.[100] In addition, other studies found that patients with psoriasis had a higher risk of poorly controlled hypertension when compared with patients without psoriasis.[106,107] This association correlates with the severity of psoriasis.[106]

Even if it is known that psoriasis is associated with hypertension, the temporal association may be difficult to be defined.[108] One large US prospective cohort study involving 777,728 female participants found that patients with hypertension had an elevated risk of developing psoriasis with a hazard ratio (HR) of 1.27 (95% CI 1.03 – 1.57).[108] However, the interpretation of this study might be limited due to some confounders not being considered (e.g. family history). Moreover, the study population also restricted the interpretation of this study because it involved only women.

Although there are a number of studies examining the relationship between psoriasis and hypertension, the mechanism is complex and remains unknown.[84,109] Moreover, a number of confounders can influence the analysis of this association. For example, patients with moderate-severe psoriasis that are treated with ciclosporin may experience hypertension which is a recognised side effect of this drug.[84] Beta-blockers which are anti-hypertensive drugs can also induce or exacerbate psoriasis.[110]

2.7.6.2 Dyslipidaemia

Dyslipidaemia is a well-established cardiovascular risk factor for coronary artery disease, stroke, MI and cardiovascular mortality.[111–114] A number of studies have shown an increased prevalence of dyslipidaemia among patients with psoriasis.[115,116] Furthermore, they are more likely to have an increased risk of hypercholesterolemia.[117] Prevalence rates of dyslipidaemia vary widely across the studies with ranges: 6.4 – 50.9% for unspecified severity of psoriasis, 4.7 – 23.9% for mild psoriasis and 6.0 – 29.9% for severe psoriasis.[101–103,118] Moreover, numerous studies have found that psoriasis is associated with a decreased level of

high-density lipoprotein (HDL), an increased level of triglyceride (TG), low density lipoprotein or very low density lipoprotein.[116,117,119–125]

It is not easy to evaluate the relationship between psoriasis and dyslipidaemia for several reasons. Firstly, the definition of dyslipidaemia is often unclear.[84] Dyslipidaemia is a broad term of abnormalities of plasma lipid levels and various studies have used this term differently with different study methods, coding systems and codes. Moreover, the selection of appropriate diagnosis codes for dyslipidaemia is also a problem for the evaluation of the association between dyslipidaemia and psoriasis. For example, a study which used the WHO International Classification of Diseases (ICD)-10 to evaluate the association between psoriasis and hyperlipidaemia included both hyperlipidaemia terms and lipoprotein deficiency terms.[126,127] Secondly, since dyslipidaemia is a component of the metabolic syndrome, it tends to co-occur with other components of the metabolic syndrome (e.g. obesity) which are also highly prevalent in patients with psoriasis.[84]

2.7.6.3 Insulin resistance and type 2 diabetes mellitus

Type 2 diabetes mellitus is a growing global concern. It is characterised by a resistance of peripheral tissue to insulin and reduced secretion of insulin from the pancreas. It is estimated that 324 million people will suffer from diabetes worldwide by 2025.[128] It is inevitable that some patients with psoriasis will also be faced with this disease. A number of studies have found that psoriasis is associated with a higher risk of diabetes.[115,129–132] This increase may be due to overproduction of Th1 cytokines in patients with psoriasis. It may promote insulin resistance.[109] Moreover, TNF-alpha, which is a crucial cytokine of psoriasis pathogenesis, can induce insulin resistance. Furthermore, it has been suggested that genetic factors may also contribute to an elevated susceptibility to type 1 and 2 diabetes in psoriasis patients.[133–135] The prevalence rates of diabetes reported vary widely ranging from 2.4 – 37.4% for unspecified or mild-moderate psoriasis and 7.5 – 41% for severe psoriasis.[105,136,137] A recent meta-analysis of observational studies reported on this association with the ORs of 1.53 (95% CI 1.16-2.04) for mild psoriasis (from four included studies) and 1.97 (95% CI 1.48-2.62) for severe psoriasis (from five included studies).[138] The included studies examining the association of diabetes according to the severity of psoriasis controlled for cardiovascular risk factors differently when calculating the ORs. All of the included studies took into account age and sex of participants[105,138–140] but only some of them controlled for other important cardiovascular risk factors such as hypertension, hyperlipidaemia, smoking, body mass index (BMI) or obesity[103,118]. This meta-analysis also examined the risk of incident diabetes in psoriasis patients. It found a significantly increased risk with a pooled relative risk (RR) of 1.27 (95% CI 1.16 – 1.40).

Some studies have shown that the greater severity of psoriasis also correlates with the likelihood of insulin resistance and diabetic complications.[122,141] Furthermore, diabetic patients with psoriasis tend to require use of more anti-diabetic drugs and have a higher risk of microvascular and macrovascular complications when compared with diabetic patients without psoriasis.[142,143] However, the results of the assessment of the association between psoriasis and diabetes may also be influenced by the use of anti-diabetic drugs. Two RCTs have shown

that metformin could decrease the severity of psoriasis and improve the components of metabolic syndrome.[144,145] Nonetheless, the interpretation of these studies is limited because they had small sample sizes (about 20 participants per group) and short duration of follow-up (12 weeks). Two other population-based observational studies have suggested that the frequent use of metformin could reduce the risk of the development of psoriasis whilst the regular use of insulin might elevate the risk of psoriasis.[146,147] Both studies controlled for a number of confounders but many confounders relating to the development of psoriasis (e.g. alcohol consumption) were not considered.

2.7.6.4 Metabolic syndrome

Metabolic syndrome is a cluster of cardiovascular risk factors including obesity, hypertension, dyslipidaemia and insulin resistance.[148] This syndrome is a predictor of the development of diabetes and CVD.[149–151] Numerous studies have reported that psoriasis patients are more likely to have metabolic syndrome and its components including hyperlipidaemia, hypertension, diabetes and obesity.[152–157] The prevalence rates of metabolic syndrome differ depending on geographic location, sex, age and ethnicity.[148] It is estimated that the prevalence of metabolic syndrome in the general population ranges from 14.2 - 23.7%[158,159] and this syndrome is more prevalent among patients with psoriasis and it increases with the greater severity of psoriasis.[115,122,160–165] According to previous studies, the prevalence of metabolic syndrome reported ranges from 16 - 46% for mild psoriasis and 26 – 65% for severe psoriasis.[105,164]

The range of prevalence rates of metabolic syndrome in patients with psoriasis observed is very wide. The causes of this difference may be due to different study populations, severity of psoriasis, and geographic locations. The definition of metabolic syndrome used in different studies may also contribute to this difference. The WHO and the European group for the study of insulin resistance (EGIR) require insulin resistance as an absolute requirement for the definition of metabolic syndrome.[166,167] However, the definition by the EGIR can be applied to only patients without diabetes.[167] The National Cholesterol Education Programme: Adult Program Treatment Panel III (NCEP: ATP III) defined the definition differently. It does not require insulin resistance as an absolute requirement.[168] Thus, this definition is more applicable than the WHO and EGIR definitions and is widely used by researchers around the world.[169] Nonetheless, the cutoffs of waist circumference in this definition would not apply to all people such as Asian people.[170] The International Diabetes Federation (IDF) considered race- and sex-specific waist circumference cutoffs for defining the definition.[171] Table 2.1 shows the definitions of metabolic syndrome by these organisations.

Table 2.1 Definitions of metabolic syndrome

	WHO (1999)[166]	EGIR (1999)[167]	NCEP ATP III (2002)[168]	IDF (2005)[171]
Absolute requirement	Insulin resistance[a] [impaired glucose intolerance, impaired fasting glucose type 2 diabetes or other evidence of insulin resistance (under hyperinsulinaemic, euglycaemic conditions, glucose uptake < 25th percentile for background population under investigation)]	Insulin resistance or fasting hyperinsulinaemia (plasma insulin > 75th percentile in non-diabetic population)	None	Central obesity (waist circumstance)[c]: ≥ 94 cm (male), ≥ 80 cm (female) for Europids sub-Saharan Africans, eastern Mediterranean and middle east (Arab) population; ≥ 90 cm (male), ≥ 80 cm (female) for South Asians, Chinese, ethnic south and central Americans; and ≥ 85 cm (male), ≥ 90 cm (female) for Japanese
Criteria	Insulin resistance or diabetes plus two of the five criteria below	Insulin resistance or fasting hyperinsulinaemia (plasma insulin > 75th percentile in non-diabetic population)[c] plus two of the four criteria below	At least three of five criteria below	Obesity plus two of the four criteria below
Obesity	Waist/hip ratio: > 0.90 (male), > 0.85 (female) or BMI > 30 kg/m^2	Waist circumstance: ≥ 94 cm (male), 80 cm (female)	Waist circumstance: > 102 cm (> 40 inches) (male), > 88 cm (> 35 inches) (female)	Central obesity already required

	WHO (1999)[166]	EGIR (1999)[167]	NCEP ATP III (2002)[168]	IDF (2005)[171]
Hyperglycaemia	Insulin resistance already required	Fasting plasma glucose ≥ 6.1 mmol/l	Fasting plasma glucose ≥ 100 mg/dl	Fasting plasma glucose ≥ 100 mg/dl (5.6 mmol/l) or previous diagnosis of type 2 diabetes
Dyslipidaemia	TG ≥ 150 mg/dl (1.7 mmol/l) or HDL cholesterol < 35 mg/dl (0.9 mmol/l) (male), < 39 mg/dl (1.0 mmol/l) (female)	TG > 2.0 mmol/L, HDL cholesterol < 1.0 mmol/l or pharmacologic treatment	TG ≥ 150 mg/dl	TG ≥ 150 mg/dl (1.7 mmol/l) or pharmacologic treatment
Dyslipidaemia (second, separate criteria)			HDL cholesterol< 40 mg/dl (male), < 50 mg/dl (female)	HDL: < 40 mg/dl (1.03 mmol/l) (male), <50 mg/dl (1.29 mmol/l) (female) or pharmacologic treatment
Hypertension	≥ 140/90 mmHg	>140/90 mmHg or pharmacologic treatment	≥ 130/85 mmHg	≥ 130 mmHg systolic blood pressure or ≥ 85 mmHg diastolic blood pressure or pharmacologic treatment
Other criteria	Microalbuminuria[b]			

Notes: [a] other evidence includes euglycemia clamp studies; [b] Urinary albumin excretion of ≥ 20 mcg/min or albumin-to-creatinine ratio of ≥ 30 mg/g; [c] If BMI is > 30kg/m², central obesity is assumed and waist circumference is not required to be measured.

Abbreviations: BMI, body mass index; EGIR, European group for the study of insulin resistance; HDL, high-density lipoprotein; IDF, International Diabetes Federation; NCEP: ATP III, National Cholesterol Education Programme: Adult Program Treatment Panel III**;** TG, triglyceride; WHO, World Health Organisation

Resistance to insulin can be elevated by inflammatory cytokines (e.g. TNF-alpha) which are also related to the pathogenesis of psoriasis.[148,172] Moreover, patients with psoriasis have an elevated level of leptin which is also increased in obese people.[173,174] Hyperleptinaemia has been reported to be a predictor for the development of metabolic syndrome among patients with psoriasis.[174]

Several studies have reported on the association between psoriasis and metabolic syndrome. A large UK study of 44,715 participants (4,065 psoriasis patients) found that the prevalence rate of psoriasis cohort (34%) was higher than the control group (26%).[122] The overall OR was 1.41 (95% CI 1.31 – 1.51). This study classified the severity of psoriasis using BSA [2,044 patients with mild psoriasis (≤ 2% BSA); 1,377 patients with moderate psoriasis (3-10% BSA) and 475 patients with severe psoriasis (> 10% BSA)]. The results showed that the risk of developing metabolic syndrome was related to the severity of disease. The ORs for metabolic syndrome increased with the greater severity of psoriasis [OR 1.22 (95% CI 1.11–1.35) for mild psoriasis and OR 1.98 (95% CI 1.62–2.43) for severe psoriasis]. However, this relationship is in contrast to a small Italian case-control study of 338 patients with psoriasis and 334 outpatients with other skin diseases conducted in a dermatology department.[156] This study classified the severity of psoriasis using PASI, BSA and physician global assessment (PGA). This study found a significant association between psoriasis and metabolic syndrome [OR 1.65 (95% CI 1.16 – 2.35)] but this association was not significantly different according to the severity of psoriasis. Nevertheless, these two studies had many major differences which might have an effect on the assessment such as the sizes of studies and methods of classification of the severity of psoriasis. However, the prevalence rates of metabolic syndrome for patients with psoriasis (30.1%) and without psoriasis (20.6%) in the Italian study were similar to those of the UK study.

The assessment of the association between psoriasis and metabolic syndrome is not straightforward as other factors may also influence the development of metabolic syndrome; for instance, some systemic psoriasis therapies can exacerbate or precipitate facets of the metabolic syndrome (retinoids can increase the risk of dyslipidaemia while etanercept, adalimumab, infliximab and anti-IL-12/23 agents may induce weight gain).[84]

2.7.6.5 Obesity

Obesity is an important cardiovascular risk factor. The WHO classifies people who have 25.0 – 29.9 and ≥ 30.0 kg/m^2 BMI as overweight and obese, respectively.[117,160,175–177] Obesity is a global concern since it is associated with a number of serious comorbidities such as hypertension, dyslipidaemia, type 2 diabetes mellitus, coronary heart disease and stroke.[178,179] Being overweight or obese can also lead to an increased risk of mortality.[180]

A number of epidemiological studies assessing the relationship between psoriasis and obesity have found that psoriasis is associated with an elevated prevalence of obesity.[115,117,160,176,177] In addition, the severity of psoriasis also appears to be associated with the degree of obesity.[181,182] In published studies, the prevalence of obesity ranged from 14 – 17% for mild psoriasis and 20 – 42% for moderate-severe psoriasis.[103,154,183] For overweight,

the prevalence ranged from 35 – 40% for mild psoriasis and 20 – 42% for moderate-severe psoriasis.[118,137,154,183]

A systematic review and meta-analysis of 16 observational studies with a total study population of 21 million (201,831 patients with psoriasis) found a significant association between psoriasis and obesity.[184] Patients with greater severity of psoriasis had a higher association between psoriasis and obesity; the pooled ORs for obesity were 1.46 (95% CI 1.17 – 1.82) among patients with mild and 2.23 (95% CI 1.63 – 3.05) among patients with severe psoriasis. An incidence study in this review reported that psoriasis was related to new-onset obesity with a HR of 1.18 (95% CI 1.14 – 1.23).[129]

2.7.6.6 Cigarette smoking and alcohol consumption

Smoking and alcohol consumption are well-known cardiovascular risk factors. Several studies have shown that patients with psoriasis smoke and consume alcohol more often than patients without psoriasis.[185,186] The prevalence of current smokers among patients with psoriasis has been reported widely and varies from 14 to 51.3%.[140,187] Definitions of alcohol consumption across studies are heterogeneous making direct comparisons between studies difficult, but the highest reported rate was 85.8% among patient with psoriasis.[188] Although both of these behavioural factors are more common in patients with psoriasis, it still remains unclear whether they may elevate the risk of developing psoriasis or occur as a result of psoriasis related to psychological stress, or both.[189] A recent meta-analysis found that smoking often preceded psoriasis and suggested a possible a dose-effect of cigarette smoking intensity and duration of psoriasis.[185] Patients with psoriasis who smoke have an increased number of peripheral blood Th17 cells which are part of psoriasis pathogenesis.[190] Thus, this may partially explain an elevated risk of psoriasis in smokers.[189]

2.7.7 Cardiovascular disease

The association between psoriasis and the risk of CVD has been investigated for over 20 years.[191] However, the association is still unclear as many patients with psoriasis tend to have other cardiovascular risk factors as described above. In addition, unhealthy lifestyle habits such as smoking and excess alcohol consumption may influence the development of CVD in patients with psoriasis.[192,193] Inflammation is a central theme supporting a theoretical association between psoriasis and CVD.[84] Inflammatory cells and proinflammatory cytokines can have an influence on both the development of psoriasis lesions and the breakdown of atherosclerosis.[194]

Psoriasis and atherosclerosis have similar crucial mediators. Thus, the mechanism of these conditions may be linked.[84] The pathogeneses of both conditions are linked by Th1 and Th17 cells and their cytokines.[195] Moreover, they also share a common pattern of T-cell activation.[194] Activated T-cells near inflammation areas can produce type 1 cytokines such as TNF-alpha. TNF-alpha is an inflammatory cytokine which is related to the pathogenesis of

psoriasis and atherosclerosis.[109,196] Furthermore, both diseases are also associated with other common cytokines including IL-1, Il-6, Il-10, leptin and adiponectin.[197]
C-reaction protein (CRP) is a marker of systemic inflammation which correlates with atherosclerosis and CVD. The interactions between proinflammatory cytokines IL-1, IL-6 and TNF-alpha result in an elevated CRP [198] which is associated with adverse CVEs [199,200] and cardiovascular risk factors such as smoking, obesity and diabetes.[201] Moreover, it was found that an increased CRP level correlates with the greater severity of psoriasis.[202,203]

Another possible mechanism of the association between psoriasis and atherosclerosis is that keratinocytes produce vascular endothelial growth factor (VEGF), which is a mitogen for endothelial cells.[204–206] Furthermore, VEGF is positively related to the severity of psoriasis and elevated intimal media thickness.[204–206]

Patients with psoriasis have a low level of folate due to a rapid turnover and increased keratinocyte activity. It subsequently results in a higher homocysteine level compared with people without psoriasis.[202,207] Hyperhomocysteine is an independent risk factor for CVD, peripheral vascular disease and cerebrovascular disease.[208] However, the relationship between the severity of psoriasis and level of homocysteine is uncertain.[202]

There are a number of studies examining the association between psoriasis and CVD. They reported that the prevalence ranged from 4.6 – 7.8% for CVD and 3.1 – 6.5% cerebrovascular events among patients with psoriasis.[209] However, the relationship between psoriasis and CVD is still unclear as several studies have reported a positive association, whilst some studies have not found this association.

Gelfand et al. conducted a population-based cohort study with a mean follow-up of 5.4 years in order to assess the risk of MI. [154] They found that psoriasis patients (n=130,976) had a higher incidence of MI than that in the control group (n=556,995) and indicated that this corresponded to the severity of the disease. The incidence of MI in severe, mild psoriasis and control patients was 5.13 (95% CI 4.22 - 6.17), 4.04 (95% CI 3.88 - 4.21) and 3.58 (95% CI 3.52 - 3.65) per 1,000 person-years, respectively. The RR of MI among younger psoriasis patients aged 30 years was 1.21 (95% CI 1.14 - 1.46) for mild and 3.10 (95% CI 1.98 - 4.86) for severe psoriasis. Similarly, in the older group aged 60 years, the RR of MI was 1.08 (95% CI 1.03 - 1.13) for mild and 1.36 (95% CI 1.13 - 1.64) for severe psoriasis. It can be seen that the RRs for MI in young psoriasis patients were significantly higher than those in older psoriasis patients. The results of this study appeared to suggest that psoriasis may be an independent risk factor for MI.[210] There are a number of limitations to this study that may influence the results presented: namely, there were no restrictions on patients entering the cohort having previously experienced CVEs, patients were categorised as having severe psoriasis if they had ever received azathioprine (which is not an established treatment for severe psoriasis), and no adjustments were made for a number of established cardiovascular risk factors, such as psoriatic arthritis (a common comorbidity in patients with psoriasis as described earlier). Moreover, this study included severe

psoriasis patients treated with methotrexate, oral retinoids and ciclosporin. These medications may have an effect on the CVD outcome since methotrexate is associated with a lower incidence of CVD[211]; and oral retinoids and ciclosporin may induce cardiovascular factors such as hypertension and hyperlipidaemia.[212,213] However, several other epidemiological studies have reported a higher likelihood of MI, stroke, cardiovascular deaths, collectively termed "major adverse CVEs (MACEs)" in patients with psoriasis.[5,137,214,215] Nevertheless, a few studies did not observe a significant association between psoriasis and MACEs.[216,217]

For example, a recent inception cohort study with a follow-up mean of 5.2 years (2015)[216], which used the UK population-database (Clinical Practice Research Datalink: CPRD) examined the relationship between psoriasis and a risk of major CVEs (i.e. MI, acute coronary syndrome, unstable angina and stroke). This study analysed data of 48,523 patients with psoriasis and 208,187 controls. The results of the study showed that psoriasis and severe psoriasis were not significantly associated with an increased risk of major CVEs after adjusted for known cardiovascular risk factors. The HRs of major CVEs for psoriasis and severe psoriasis were 1.02 (95% CI 0.95 - 1.08) and 1.28 (95%CI 0.96 - 1.69), respectively.

Several meta-analyses have been conducted to examine the association between psoriasis; and CVD and/or cardiovascular risk factors as shown in Table 2.2. Most reviews found that psoriasis was associated with an increased risk of CVD overall or some cardiovascular risk factors such as diabetes, hypertension, dyslipidaemia, obesity and metabolic syndrome.[115,218] Furthermore, psoriasis was found to be associated with an elevated risk of stroke and/or MI.[219,220] The results of a meta-analysis by Samarasekera et al. (2013) suggested that severe psoriasis was significantly related to an elevated risk of stroke but not significantly increased the risk of MI.[221] They also suggested that most of the included studies accounted for only some key cardiovascular confounders (age, sex, smoking, alcohol consumption, obesity, hyperlipidaemia, hypertension or diabetes). This confounding might lead to biased results. Moreover, another meta-analysis reported that the severity of psoriasis corresponded to the degree of risk of stroke and MI.[220]

Table 2.2 Summary of meta-analyses examining the association between psoriasis and cardiovascular disease and cardiovascular risk factors

Authors (year of publication)	Study design	Study population	Results	Conclusions and comments
Pietrzak et.al. (2013)[218]	Meta-analysis 4 case–control and 10 cohort studies published during 2006 - 2011	Psoriasis patients vs non-psoriasis patients	Cardiovascular events OR = 1.28 (95% CI 1.18–1.38)	**Conclusion** Psoriasis was significantly associated with an increased risk of CVEs.[218] **Comments** This meta-analysis had major limitations due to quality of the original studies included in the review. Some studies did not provide information on cardiovascular risk factors such as smoking and obesity. Moreover, anti-psoriatic therapies such as methotrexate may reduce the frequency of CVEs which was often not considered.[218] Therefore, the results of assessing the association between psoriasis and CVD may be biased. **Note** The definition of CVEs was defined as MI, ischemic heart disease, cerebral ischemic stroke, sudden cardiac death etc.

Authors (year of publication)	Study design	Study population	Results	Conclusions and comments
Miller et. al. (2013) [115]	Meta-analysis of 75 observational studies (cross-sectional, case-control and cohort) published before 25 October 2012	Psoriasis patients vs non-psoriasis patients	**Associations** CVD overall: OR = 1.4 (95% CI 1.2 - 1.7) Ischemic heart disease: OR = 1.5 (95% CI 1.2 - 1.9) Peripheral vascular disease: OR = 1.5 (95% CI 1.2 - 1.8) Atherosclerosis: OR = 1.1 (95% CI 1.1 - 1.2) Diabetes: OR = 1.9 (95% CI 1.5 - 2.5) Hypertension: OR = 1.8 (95% CI 1.6 - 2.0) Dyslipidaemia: OR = 1.5 (95% CI 1.4 - 1.7) Obesity by BMI: OR = 1.8 (95% CI 1.4 - 2.2) Obesity by abdominal fat: OR = 1.6 (95% CI 1.2-2.3) Metabolic syndrome: OR = 1.8 (95% CI 1.2 - 2.8) **No associations** Cerebrovascular disease: OR = 1.1 (95% CI 0.9 - 1.3) Cardiovascular mortality: OR = 0.9 (95% CI 0.4-2.2)	**Conclusions** Psoriasis was related to ischemic heart disease and cardiovascular risk factors. Hospital-based studies and psoriatic arthritis showed the strongest associations but population-based studies did not demonstrate a significant association apart from dyslipidaemia.[115] Psoriasis was significantly related to an increased risk of CVD overall, peripheral vascular disease, atherosclerosis, diabetes, hypertension, dyslipidaemia, obesity and metabolic syndrome. Psoriasis was associated with an increased risk of cerebrovascular disease and a decreased risk of cardiovascular mortality but these associations were not significant. **Comments** Potential selection bias was identified in this meta-analysis since the majority of studies analysed were hospital-based and the associations were found in these

Authors (year of publication)	Study design	Study population	Results	Conclusions and comments
				studies but not found in the general population based studies except dyslipidaemia.[115] CVD is more common in psoriatic arthritis patients.[222] It may have an influence on examining the association between CVDs and psoriasis. Unmeasured confounders such as smoking and diabetes were not accounted for in the original studies examining cardiovascular mortality. These confounders could increase the prevalence of cardiovascular in patients with psoriasis. Cross-sectional and case-control studies tend to have a greater chance of bias.[223,224]
Xu and Zhang (2012)[219]	Meta-analysis 7 cohort studies published before March 2012	Psoriasis patients vs non-psoriasis patients	Stroke and MI RR = 1.2 (95% CI 1.1 – 1.31) **Subgroup analysis** Stroke RR = 1.21 (95% CI 1.04 – 1.4) MI RR = 1.22 (95% CI 1.05 – 1.42)	**Conclusions** Psoriasis was associated with a 20% increase in the risk of stroke and MI.[219] **Comments** There were variations in methods of outcome assessment and adjusting for covariates. These variations may have an

Authors (year of publication)	Study design	Study population	Results	Conclusions and comments
				effect on the results of this meta-analysis.
Samarasekera et al. (2013)[221]	Systematic review and meta-analysis of 14 cohort studies published before 2012	Psoriasis patients vs the general population	CVD mortality Mild psoriasis: RR = 1.03 (95% CI 0.86 - 1.25) Severe psoriasis: RR = 1.37 (95% CI 1.17 - 1.60) MI All psoriasis: RR = 1.40 (95% CI 1.03 – 1.89) Mild psoriasis: RR = 1.34 (95% CI 1.07 – 1.68) Severe psoriasis: RR = 3.04 (95% CI 0.65-14.35) Stroke All psoriasis: RR = 1.13 (95% CI 1.01 – 1.26) Mild psoriasis: RR = 1.15 (95% CI 0.98 – 1.35) Severe psoriasis: RR = 1.59 (95% CI 1.34 - 1.89)	**Conclusion** Severe psoriasis was significantly associated with an increased risk of CVD mortality and stroke. Severe psoriasis was also associated with an increased risk of MI but this association was not significant. **Comment** It is unclear whether psoriasis results in CVD risk because the majority of studies reviewed failed to adjust for all key traditional cardiovascular risk factors.[221]
Armstrong et.al. (2013)[220]	Systematic review and meta-analysis 9 cohort studies and nested case-control studies published during 1 January 1980 - and 1 January 2012	Mild and severe psoriasis patients vs non-psoriasis patients	Cardiovascular mortality Severe psoriasis: RR = 1.39 (95% CI 1.11 - 1.74) MI Mild psoriasis: RR = 1.29 (95% CI 1.02 - 1.63) Severe psoriasis : RR = 1.70 (95% CI 1.32 - 2.18) Stroke Mild psoriasis: RR = 1.12 (95% CI 1.08 - 1.16) Severe psoriasis : RR = 1.56 (95% CI 1.32 - 1.84)	**Conclusions** Patients with mild psoriasis had a 29% and 12% increase in the risks of MI and stroke, respectively while patients with severe psoriasis had higher associations with MI (70%) and stroke (56%). Moreover, severe psoriasis was related to a 39% increase in cardiovascular mortality.

Authors (year of publication)	Study design	Study population	Results	Conclusions and comments
				Comment A major strength of this meta-analysis was the original studies had large sample sizes. In addition, if there were more than one studies reporting the same or largely overlapping participants for the same outcome, the study with the highest number of person-years of follow-up was selected for this study.[220] The levels of covariate adjustment were different among studies analysed. It might result in the possibility of residual confounding.[220]

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; CVE, cardiovascular events; MI, myocardial infarction; OR, odds ratio; RR, relative risk

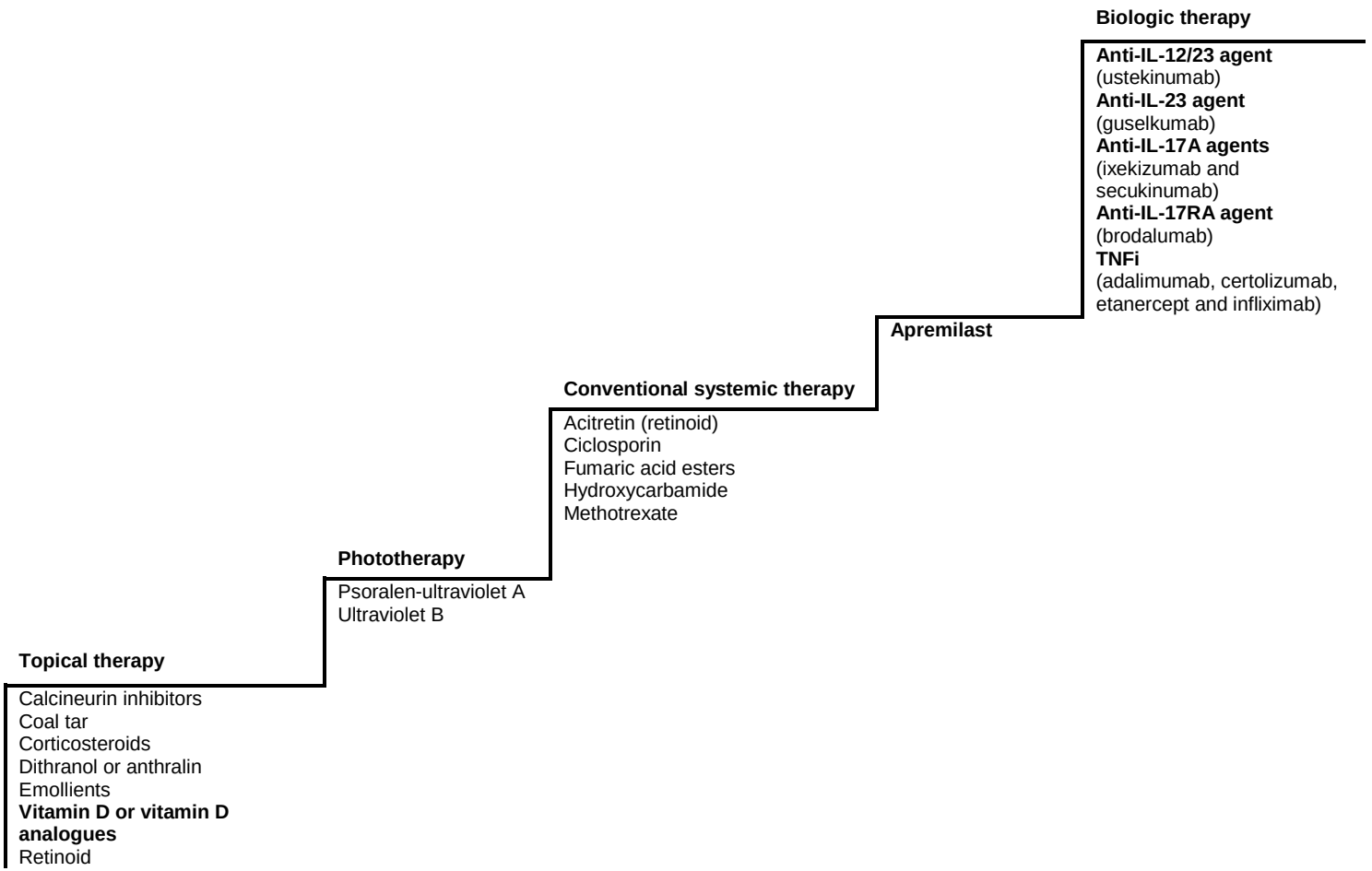
2.8 Treatment of psoriasis

Due to the diverse clinical presentation of psoriasis, approaches to treatment should be tailored to the individual on the basis of the severity of psoriasis, clinical subtypes, comorbidities and patient preference.[225,226] Psoriasis treatment is stepwise as shown in Figure 2.1. In Figure 2.1, within each category, the therapies are listed alphabetically and do not represent any ranking.[225] The treatments can be used as monotherapy or as combination therapies.[226] Patients with psoriasis are not required to transition through each step, although specific requirements may need to be met to initiate certain treatments (such as biologic therapies). The combination treatments may be from multiple rungs of the psoriasis treatment ladder.[225] Emollients are considered as basic therapy of psoriasis.[227] However, there are no placebo-controlled trials supporting their use. Emollients are used to reduce scaling, limit painful fissuring, and pruritus.[228]

This thesis focuses on the psoriasis treatment in the UK guidelines [(NICE, SIGN and British Association of Dermatologists (BAD)] at the time the thesis was prepared.

Figure 2.1 Psoriasis treatment ladder

This figure is adapted from a review by Jabbar-Lopez et.al, 2014[225]



Abbreviations: IL, interleukin; TNFi, tumour necrosis factor-alpha inhibitors

2.8.1 Topical therapies

Approximately 80% of patients with psoriasis have mild-to-moderate severity. Topical therapies play a crucial role in the treatment of psoriasis in these patients. Patients with psoriasis often start their treatment with topical corticosteroids, vitamin D_3 preparations, or a combination of the two.[229]

2.8.1.1 Topical corticosteroids

Topical corticosteroids are the most widely prescribed treatment for psoriasis worldwide.[226] Topical corticosteroids are divided into four potency groups in the UK (mild, moderate, potent and very potent)[230] and seven potency groups in the US [superpotent (class 1) – the very low potency (class 7)].[229] The strength is categorised according to their ability to induce vasoconstriction.[230] The potency can be enhanced by chemical modification.[226] Moreover, the vehicle of topical corticosteroid can affect percutaneous absorption and therapeutic efficacy. Topical corticosteroids in an ointment preparation may be more potent with the same drug than in a cream, lotion, or other preparations.[229] In choosing a topical corticosteroid for the treatment of psoriasis, healthcare professionals should decide on the desired potency on the basis of the severity and location of skin lesions and the vehicle on the basis of lesion types to be treated, need for hydration or effect of drying, location and potential for irritation as a result of components of the vehicle.[229] Lotions are appropriate for the face. Ointments are suitable for dry lesions and gels work well for hairy areas or a drying effect for a wet lesion. Potent and superpotent topical corticosteroids should not be used on the face and intertriginous areas owing to the risk of skin atrophy.[229]

In a systemic review of 41 randomised placebo-controlled trials and 28 randomised head-head studies, potent and very potent topical corticosteroids were found to be more effective for psoriasis treatment than mild to moderate potency corticosteroids.[231] However, a major limitation of this review was the short duration of the clinical trials. Therefore, this review could not explore long-term adverse effects of these products. Patients receiving treatments for long periods may experience local side effects e.g. skin atrophy, telangiectasia, striae distensae and purpura; and systemic side effects e.g. Cushing's syndrome and hypothalamic-pituitary-adrenal axis suppression.[232] These side effects tend to occur in patients treated with high potency corticosteroids. Psoriasis treatment guidelines recommend that such treatments should not be used more than twice daily (50 mg maximum/week) for up to two consecutive weeks and not used on the face or intertriginous areas. To minimise these side effects, various regimens are used e.g. use at weekends only, conjunction with non-steroidal medicines, and transition to weaker potency products.[226] The results of a double-blind multicentre trial demonstrated that three applications of betamethasone propionate one day/week could maintain clinical response in 60% of patients with psoriasis compared with 20% of patients with psoriasis receiving placebo; and was safe for up to six months.[233]

2.8.1.2 Vitamin D_3 derivatives

Vitamin D_3 derivatives are the first-line therapy for plaque psoriasis.[226] There are three vitamin D_3 derivatives currently available on the UK market, namely calcitriol, calcipotriene and tacalcitol. These medications bind to vitamin D receptors which consequently bind to the vitamin D response element region on target genes. This leads to inhibition of cellular proliferation and inflammation and stimulation of differentiation.[234]

Calcitriol

Calcitriol is the natural form of vitamin D_3. It can affect calcium metabolism. Thus, if it is applied excessively, it may cause hypercalcemia and hypercalciuria. It is available as an ointment preparation in the US and Europe.[229]

Calcipotriene

Calcipotriene or calcipotriol is a synthetic form of calcitriol. Patients treated with calcipotriene are less likely to develop hypercalcemia. Calcipotriene is available in ointment, cream, and solution preparations in the US, Europe and Asia. [229]

Tacalcitol

The structure of tacalcitol slightly differs from calcitriol. However, both medications have similar affinity for vitamin D receptors and efficacy. Tacalcitol can induce hypercalcemia at equivalent doses to calcitriol. Tacalcitol is available in the forms of an ointment, cream, lotion and solution in Japan and an ointment in Europe.[229]

A Cochrane meta-analysis of 177 RCTs involving 34,808 participants found that calcipotriol [17 RCTs; standardised mean difference (SMD) -0.96, 95% CI -1.12 to -0.77], calcitriol (7 RCTs; SMD -0.92, 95% CI -1.54 to -0.29), and tacalcitol (4 RCTs; SMD -0.73, 95% CI -1.09 to -0.37) significantly improved psoriasis severity when compared with placebo.[235] The NICE found that combination therapy with a vitamin D_3 derivative and corticosteroids had greater efficacy than either alone.[45,225] Given this, the NICE recommends that calcitriol, calcipotriene, or tacalcitol should be used as first-line therapy in combination with a potent topical corticosteroid but vitamin D_3 and its analogues are not effective for the management of nail psoriasis.[45,225] An initial clinical response is normally seen after two – four weeks of the treatment. Topical therapy alone may be sufficient for most patients with mild-moderate psoriasis. In patients with severe psoriasis, topical therapy including vitamin D_3 derivatives is an important adjunct to other therapies such as phototherapy and systemic therapies including biologic therapies. These combination therapies may allow reduced doses of systemic therapies.[236]

Many reviews and guidelines consider the class of vitamin D_3 derivatives as a whole but a systematic review of 37 RCTs involving 6,038 patients suggests calcipotriol has greater efficacy than calcitriol or tacalcitol for the management of chronic plaque psoriasis.[237] For psoriasis affecting sensitive areas (genitals, face and flexures), the NICE and SIGN recommend a short-term course (one – two weeks/month) of mild or moderately potent topical corticosteroids as first-line therapy.[45,51] If they are ineffective or not well tolerated, vitamin D_3 topical, tacrolimus ointments and calcineurin inhibitors should be considered.[45,51]

Thirty per cent of patients treated with vitamin D_3 derivatives may experience lesional or perilesional skin irritation including symptoms of pruritus, burning, peeling, dryness and erythema. These manifestations are often reduced with ongoing therapy.[232,237] Irritation is usually self-limiting and resolved when these products are discontinued.[238] Hypercalcaemia and parathyroid suppression are rare adverse effects of treatment as serum and urine calcium concentrations can be raised by these products. For example, when calcipotriol ointment is applied for more than 300 g/week, it can cause severe hypercalcemia and hypercalciuria[239] but they do not occur when the dose is less than 100 g/week.[240] These products should not be used by patients with calcium metabolism disorders. Patients with renal disorders may be at higher risk of development of hypercalcemia.[229] Table 2.3 describes the weekly dose recommended in order to avoid effects on calcium concentrations.

Table 2.3 Maximum weekly recommended dose for vitamin D_3 derivatives[229,241]

Medication	Preparations	Maximum recommended dose
Calcitriol	Ointment	630 mcg/week
Calcipotriol	Ointment, cream and solution	5,000 mcg/week
Tacalcitol	Ointment, cream, solution and lotion	280 mcg/week

2.8.1.3 Topical retinoids

Tazarotene is the only licensed topical retinoid (a vitamin A derivative) for the management of plaque psoriasis. Moreover, this medication may be useful for palmoplantar and nail psoriasis.[229] Tazarotene reduces inflammation and normalises the abnormal keratocyte hyperproliferation and differentiation in psoriasis.

Tazarotene is available in gel and cream forms. When it is used as monotherapy (once daily dosage, usually at bedtime), it is only moderately effective.[242] Therefore, it is predominantly used in combination.[243] Use in combination therapy with a mild – high potency corticosteroid can improve efficacy and decrease irritancy and the atrophogenic potential of corticosteroids. Three times a week use of tazarotene with two times a week of superpotent topical corticosteroid may maintain improvement long-term.[228] Use of tazarotene in conjunction with broadband or narrowband ultraviolet B (UVB), or psoralen and ultraviolet A (PUVA) phototherapy can improve efficacy and reduce the total dose of ultraviolet radiation.[228]

Tazarotene is of teratogenic potential. Therefore, it should not be given during pregnancy and restriction for use in women of childbearing potential with localised plaques only.[226] Up to 20% of patients may experience local skin irritation.[244] This effect can be reduced by using the cream preparation, low concentration, application on alternate days, short contact, and use in combination with a mid or high potency topical corticosteroid in the morning.[242,244,245]

2.8.1.4 Calcineurin inhibitors

Calcineurin inhibitors are classified as immunomodulators which include tacrolimus and pimecrolimus. Topical calcineurin inhibitors bind to macrophilin-12. Then, they inhibit the calcium-dependent phosphate calcineurin. This lead to inhibiting translocation of nuclear factor of activated T-cell (NFAT) and also reducing cytokine synthesis which plays an important role in the pathogenesis of psoriasis. However, these products are not licenced for the treatment of psoriasis in the UK and the US.[229,246] Nevertheless, these medications are frequently used off-licence for the treatment of psoriasis in the UK.[247] Their efficacy in the psoriasis treatment is limited. Since their molecules are large, it has a problem with penetration through the thick scale.[248] They can be used in under occlusion, on the face, intertriginous area and genitals.[249,250] An advantage of these products is that they do not cause skin atrophy.[226]

2.8.1.5 Dithranol

The use of dithranol has reduced considerably for the treatment of psoriasis. As monotherapy, dithranol has lower efficacy than topical corticosteroids or vitamin D_3 derivatives.[231] However, when it is used in combination with UVB phototherapy according to the regimen proposed by Ingram, it shows greater improvement than UVB alone.[251] The use of dithranol in conjunction with intermittent high potency topical corticosteroids can minimise irritation[252] and improves efficacy without shortening duration of remission.[253] In addition, a twice-daily dose of calcipotriol in conjunction with short contact 2% dithranol substantially increases the efficacy and tolerability of dithranol.[254] Short contact applications of high-dose dithranol (for up to 30-60 minutes/day) are as effective as longer applications and twice daily dosage of calcitriol ointment.[226] A disadvantage of dithranol is that it can markedly irritate and stain skin, clothing and furniture.[226]

2.8.1.6 Coal tar

Coal tar has been used for psoriasis treatment for more than one-hundred years. It is available as ointment, shampoo, solution and crude coal tar (the most effective form). Traditionally, coal tar has been used in hospitals or in day treatment centres as part of the Goeckerman regimen whereby its use in addition to UVB has better efficacy than UVB alone.[255] The results of one trial found that 0.005% calcipotriol ointment was effective as 5% coal tar in conjunction with sun exposure in the treatment of stable plaque psoriasis after 8 week of treatment.[256]

Disadvantages of coal tar are that it can cause skin irritation, folliculitis, odour, and staining clothing.[257] Owing to other better anti-psoriatic treatments being available, coal tar has declined in use.[228]

2.8.2 Phototherapies

If psoriasis fails to be controlled by topical therapies, phototherapy may be offered to patients. Traditionally, patients with moderate-to-severe psoriasis would be treated with photochemotherapy with PUVA, although the use of PUVA in recent years has been declining. UVA wavelength approximated 311 nm is known to have anti-psoriatic activity, but excessive exposure can induce carcinogenicity. Thus, narrowed-band UVB (NBUVB) using this wavelength is a preferred choice at present and is commonly offered in hospital dermatology departments. Patients receive treatment approximately three times a week for about 20 treatments. NBUVB provides high efficacy at clearing psoriasis plaques but its benefit depends on the duration of disease-free remission ranging from many months to up to a year.[40]

Erythema is the most common short-term side effect of NBUVB. This side effect can be minimised by careful dosimetry. Its long-term risks comprise photodamage as well as a possible dose-related risk of skin cancer. The risks of PUVA are greater. The important side effects are an elevated risk of skin cancer (especially squamous cell carcinoma and melanoma), photodamage and premature ageing skin.[40]

2.8.3 Systemic therapies

Systemic therapies are the mainstay of treatment for moderate-to-severe psoriasis and patients unresponsive to topical therapies and phototherapy. They consist of conventional systemic therapies and biologic therapies. Patients who have not tolerated or are unresponsive to conventional systemic therapies will subsequently use biologic therapies.[226]

2.8.3.1 Conventional systemic therapies

Methotrexate

Methotrexate is a folic acid antagonist which has anti-proliferative, anti-inflammatory and immunosuppressive properties.[258] It interferes with purine synthesis and thereby inhibits deoxyribonucleic acid (DNA) synthesis and cell replication. Moreover, it has specific T-cell suppressive activities. Methotrexate is the most widely used systemic therapy and has traditionally been regarded as a “gold standard” for the treatment of moderate-severe psoriasis and psoriatic arthritis.[226,258]

A multicentre RCT conducted in Germany, France, the Netherlands and the UK involved 120 patients with moderate-severe psoriasis. It found that subcutaneous (SC.) methotrexate was superior to placebo.[259] At week 16, methotrexate and placebo groups achieved a PASI 75 in 41% (37/91) and 10% (3/29) in patients with psoriasis, respectively. Moreover, oral methotrexate was also compared with biologic therapies in other RCTs.[260,261] The first study involving 271 patients with moderate-severe plaque psoriasis found that methotrexate showed inferior efficacy to adalimumab but superior to placebo at week 16.[260] The second study involving 868 patients with moderate-severe psoriasis found that methotrexate was less efficacious than infliximab.[261]

Methotrexate is usually prescribed as a single weekly oral dose or three-divided dose schedule over 24 hours, after a 2.5 - 5 mg test dose, in a dose range of 7.5 – 22 mg/week depending on clinical response. Folic acid (1 - 5 mg oral daily) is often added in order to prevent stomatitis and macrocytic anaemia and reduce gastrointestinal symptoms e.g. nausea, vomiting and anorexia.[262] However, this may decrease the efficacy of methotrexate.[263] Some clinicians recommend not administering folic acid on the day patients receiving methotrexate.[258] Patients should be provided with the lowest effective dose of methotrexate by tapering the dose approximately 2.5 mg/month, when stability or adequate clearance is achieved.[226]

Since methotrexate can cause serious side effects, it is necessary to carefully select and monitor patients. In particular, methotrexate is teratogenic and therefore contraindicated during pregnancy and women should not be pregnant for at least three months after discontinuing methotrexate treatment.[264] Male patients whose partners are considering conception should not take methotrexate during this time. Another serious side effect is myelosuppression which is the most common cause of death due to methotrexate. Methotrexate can cause leucopenia, thrombocytopenia and anaemia. It is usually dose-dependent. Idiosyncratic myelosuppression rarely occurs. This type occurs at the early stage during the treatment and tends to happen in patients with advanced age, renal impairment, underlying bone marrow disease, hypoalbuminemia, concomitant medicines (such as sulphonamides, tetracyclines, dapsone and phenytoin), or folate deficiency. It is necessary to screen patients before the start of methotrexate treatment and monitor while on methotrexate in order to minimise these risks.[258] Patients on methotrexate have to be checked their blood count every three months.[265] Administration of oral daily folic acid while on methotrexate may reduce gastrointestinal and liver toxicity. However, its effect on the bone marrow toxicity remains unclear at present.[266,267]

Methotrexate can cause pulmonary fibrosis but this event is rare and less common in psoriasis than rheumatoid arthritis.[268] However, it is more commonly related to a high dose of methotrexate. [258] During long-term use, methotrexate is more likely to cause liver fibrosis and cirrhosis in patients with psoriasis than in those with rheumatoid arthritis.[226] In the UK, the measurement of type III procollagen in serum every three months is used to monitor liver fibrosis or cirrhosis.[226,265]

Evidence has suggested that methotrexate may reduce the risk of CVEs including ischemic heart disease, stroke and cardiovascular deaths) in patients with psoriasis.[9,211,269–272] Since methotrexate is an anti-inflammatory drug, this may have a vascular protective effect.[273]

A Taiwanese population-based case-control study found that psoriasis patients treated with methotrexate had a lower risk of developing cerebrovascular disease with HR of 0.50 (95% CI 0.27 – 0.92) when compared with psoriasis patients not treated with methotrexate or retinoids.[274] This study also suggested that low cumulative dose of methotrexate was associated with a decreased risk of developing cerebrovascular disease when compared with non-treatment of methotrexate or retinoids [HR = 0.53 (95% CI 0.28 – 1.00)]. However, this significantly decreased association was not observed in a high cumulative dose of methotrexate. Even if this study controlled the bias due to hypertension, diabetes and

dyslipidaemia, age and sex; some important cardiovascular risk factors were not controlled such as smoking, alcohol intake and obesity.

Acitretin

The precise mechanism of action of acitretin is unclear in psoriasis. It is thought that it is associated with decreasing epidermal proliferation and inducing differentiation. [246] Acitretin is effective in the management of erythrodermic psoriasis and palmoplantar psoriasis. It is the treatment of choice for generalised pustular psoriasis.[275] In palmoplantar pustulosis, acitretin ameliorates hyperkeratosis and decreases the pustulation. Furthermore, it can be an effective maintenance treatment for chronic plaque psoriasis in patients who respond adequately. Since it is not immunosuppressive, it is useful for the treatment of severe psoriasis in patients with human immunodeficiency virus (HIV) infection.[276]

Acitretin can be safely used in combination with other treatments which may lead to a reduction in the dose of acitretin.[246] Acitretin enhances the effectiveness of phototherapy. In addition, it can be successfully combined with TNF inhibitor (TNFi) for the treatment of chronic plaque psoriasis.[277] If acitretin is used in combination with methotrexate then the liver function should be closely monitored due to the risk of hepatotoxicity.[246,278] Furthermore, acitretin can be added to ciclosporin for short-term treatment but frequent monitoring of lipids is required. In addition, it can also be used with hydroxyurea for the treatment of recalcitrant palmoplantar pustulosis.[279] Acitretin is only advised for non-pregnant women of child-bearing potential when they have no other treatment options available.

For adult patients with psoriasis, acitretin is initially administered 25 - 30 mg daily with meals for 2 - 4 weeks with the dose adjusted according to the patients' response. The typical dose of acitretin ranges from 25 - 50 mg daily. However, it can be administered for up to 75 mg for short periods in psoriasis.[241]

Acitretin should be used with caution since it may interact with a number of medicines. For instance, when it is given with the microdose progestin minipill, it interferes with the contraceptive effects.[246,276] Moreover, when it is used in combination with tetracyclines, this combination is associated with an elevated risk of increased intracranial pressure, and manifest pseudotumor cerebri.[246] Furthermore, it may influence the glucose-lowering effects of glibenclamide and may decrease phenytoin protein binding.[276] In addition, it should not be administered with other oral retinoids or with excessive vitamin A supplementation due to hypervitaminosis.[246,276]

In terms of the impact of acitretin on cardiovascular risk, there is limited evidence on this issue. However, it is acknowledged to have an adverse effect on lipid profiles. One study found that acitretin could increase serum TG and cholesterol and the relationship is a dose-dependent elevation.[280] However, these elevations could be well managed with diet and dose change.[281] Since a side effect of acitretin is hyperlipidaemia, this may result in an increased risk of CVD.

Ciclosporin

Ciclosporin is used for the short-term treatment for moderate-severe psoriasis but it has less effectiveness for the management of active psoriatic arthritis.[226,258] Ciclosporin is a

macrocyclic immunosuppressant which binds immunophilin and inhibits calcineurin phosphate-initiated activation of T-cell. It may exert a direct effect on epidermal keratocytes.[282]

Patients with severe psoriasis aged over 16 years can start treatment at an initial dose of 2.5 mg/kg daily in two divided doses. If patients have an inadequate response within one month, the dose is gradually increased to a maximum dose of 5 mg/kg. An initial dose of 5 mg/kg daily is justified if rapid control is required. If patients have an inadequate response after three months at the optimum dose, they should discontinue this medication. The duration of treatment is usually up to a maximum of one year, unless other treatment cannot be used.[241]

Ciclosporin is neither teratogenic nor myelosuppressive[283] but it requires monitoring for nephrotoxicity and hypertension.[284,285] An increased risk of non-melanoma skin cancer exists, particularly in patients previously receiving PUVA.[286] Ciclosporin is commonly used in combination therapy or in rotation with other therapies for psoriasis including low-dose methotrexate or acitretin, and other medications e.g. fumarates and biologic therapies.[287]

In terms of the impact of ciclosporin on the cardiovascular risk, it may pose an elevated risk of CVD since it can lead to hyperlipidaemia.[288] A study showed that ciclosporin did not have a cardioprotective effect.[9] Moreover, it can increase blood pressure in a manner of dose-response effect.[289] In addition, psoriasis patients treated with ciclosporin for 2 weeks had increased levels of TGs and total cholesterol and they remained increased with continued treatment.[290]

Fumaric acid esters

Fumaric acid esters are an oral treatment for psoriasis. They work by promoting a Th2-cell response instead of the Th1-dominant response found in psoriasis. This stems from inhibition of nuclear factor kappa B with enhanced T-cell apoptosis. Since fumaric acid is poorly absorbed from the gut, it should be given as an ester.[265]

The German guidelines on the treatment of psoriasis vulgaris reviewed nine studies involving fumaric acid esters and reported that 50 - 70% of patients with moderate-severe chronic plaque psoriasis could achieve a PASI 75 score after 16-week of treatment and the efficacy of this therapy was improved when it was combined with topical therapy.[291]

Fumaric acid esters have long been used in some European countries. Fumaderm® (dimethyl fumarate and monoethyl fumarate salt) has been licensed in German since 1994[292] while the UK has approved Skilarence® (dimethyl fumarate) for the treatment of moderate-severe plaque psoriasis since 2017.[246]

In terms of the impact of fumaric acid esters on the cardiovascular risk, a decreased CRP level and an increased adiponectin level (cardioprotective adipokine) were observed in psoriasis patients treated with fumaric acid esters.[293,294] However, further investigation of the impact of fumaric acid ester on CVD is still required.[189]

Table 2.4 provides information on contraindications, major toxicity, and side effects of conventional systemic therapies.

Table 2.4 Contraindications, major toxicity, and side effects of conventional systemic therapies

Therapies	Contraindications[226,258]	Major toxicity[226]	Side effects[226]	
			Others	CVD[246]
NBUVB	Xeroderma, pigmentosum, systemic lupus erythematosus	Burning, premature ageing of the skin, elevated risk of skin cancers	Erythema, burning, blistering, discomfort, post-inflammatory hyperpigmentation [295–297]	
PUVA	Photosensitivity, squamous cell carcinoma and melanoma, breastfeeding or pregnancy, aphakia, immunosuppression	Burning, premature ageing of the skin, elevated risk of melanoma and nonmelanoma skin cancers, ocular damage	Skin irritation, skin burning, tanning, nausea, headache, dizziness, psychiatric disturbance (extremely rare cases) [298]	
Methotrexate	**Absolute contradictions** Excessive alcohol consumption causing liver damage, other liver disease including hepatitis B or C, bone marrow abnormalities (anaemia, thrombocytopenia and leucopenia), immunodeficiency, nursing mothers, pregnancy, active infection **Relative contradictions** Renal insufficiency, advanced age, alcohol consumption, history of or current alcohol abuse, peptic ulcer disease, concomitant	Myelosuppression, hepatotoxicity and stomatitis	Nausea, anorexia, fatigue, headache, alopecia	**Rare – very rare** Pericardial disorders, pericarditis [241]

Therapies	Contraindications[226,258]	Major toxicity[226]	Side effects[226]	
			Others	CVD[246]
	use of hepatotoxic medications, diabetes, hyperlipidaemia, obesity, active infection			
Acitretin	Chronic hyperlipidaemia, severely impaired renal or liver function, breast-feeding or pregnant women, women of child-bearing potential who intend to be pregnant or who may fail to use reliable contraceptive methods during three years after treatment, concomitant tetracycline use	Hepatotoxicity	Mucocutaneous side effects such as hair loss, conjunctivitis, dry lips, cheilitis, dry or sticky skin,	Hyperlipidaemia especially TG levels
Ciclosporin	Uncontrolled or difficult to control hypertension, significant renal disease, malignancy, frequent infection,[258] immunodeficiency, concomitant PUVA or UVB treatment, breastfeeding or pregnancy [241]	Nephrotoxicity, hypertension, immunosuppression (increased risk of infection or malignancy)	Hypertrichosis, gingival hyperplasia, gastrointestinal intolerance, neurological disturbances	**Vascular disorders** Very common: Hypertension
Fumaric acid esters	Breast-feeding or pregnancy, abnormal haematological counts, severe gastrointestinal disease, renal impairment[225]	Haematological toxicity, hepatotoxicity, nephrotoxicity	Gastrointestinal intolerance, flushing, abdominal cramps, diarrhoea, nausea, pruritus[226]	

Abbreviations: CVD, cardiovascular disease; NBUVB, narrowed-band ultraviolet B; PUVA, psoralen and ultraviolet A; TG, triglyceride; UVB, ultraviolet B

2.8.3.2 Apremilast

Apremilast is a small molecule inhibitor of phosphodiesterase type 4 (PDE4). It acts at an earlier stage in the inflammatory cascade before biologic therapies. This leads to broad regulation of multiple inflammatory mediators. The inhibition of PDE4 prevents cyclic adenosine monophosphate (cAMP) being hydrolysed to AMP. It leads to an elevated level of cAMP. It results in down-regulating expression of a number of proinflammatory mediators such as TNF-alpha, IL-17, IL-23 and others. Furthermore, it upregulates the anti-inflammatory IL-10.[299,300]

Apremilast is an oral treatment for moderate-severe plaque psoriasis or psoriatic arthritis. It should be titrated upwards. Patients are administered with an initial dose of 10 mg on the first day. Then, the dose increases to a maintenance dose (30 mg two times/day) on day 6. The NICE recommends using this medicine when adult patients with chronic plaque psoriasis fail to response conventional systemic therapies including ciclosporin, methotrexate and PUVA or psoriasis patients are intolerant of or have a contradiction to these therapies. Moreover, they have PASI ≥ 10 and DLQI >10. Apremilast should be discontinued if patients have insufficient response to the treatment at week 16.[301]

Generally, apremilast is well tolerated.[302] Most common adverse reactions reported in patients with psoriasis or psoriatic arthritis are diarrhoea, nausea, upper respiratory tract infection and nasopharyngitis and headache. Gastrointestinal disorders occurred within 2 weeks of apremilast treatment and resolved within 4 weeks.[246] The severity of these adverse effects is mild-moderate.[246] A pooled analysis of the ESTEEM 1 and 2 and PALACE 1, 2 and 3 studies showed a low incidence of MACEs, serious infections and malignancies in patients with psoriasis and psoriatic arthritis receiving apremilast.[303]

2.8.3.3 Biologic therapies

Biologic therapies or biologics are drugs designed to block specific molecular steps in immune-mediated disease.[38] Biologic therapies have been successfully used in rheumatoid arthritis, inflammatory bowel disease and nine biologic therapies are currently approved for psoriasis treatment.[38] The target steps involving psoriasis pathology include T cells and cytokines e.g. TNF-alpha, IL-12/23 and IL-17A.[38] Biologic therapies are increasingly used for psoriasis treatment because of higher efficacy, longer drug survival times, lower toxicity and side effects compared with conventional systemic therapies (methotrexate, ciclosporin and acitretin).[304] Patients with moderate–severe psoriasis who fail to improve with other intervention are offered these therapies.[305]

Biologic therapies licensed for the treatment of psoriasis in the UK include TNFi (adalimumab, eternacept, infliximab and certolizumab) and the monoclonal antibodies (IL-12/23: ustekinumab; IL-23: guselkumab; IL-17A: secukinumab and ixekizumab; and IL-17RA: brodalumab). These empirical studies presented in this thesis focuses only on adalimumab, eternacept, infliximab, ustekinumab, secukinumab and ixekizumab since they were approved at the time studies in this thesis were undertaken. These medicines are highly effective for psoriasis treatment and since their introduction into clinical practice there has been a significant reduction in hospital admissions for psoriasis treatment.[306] The 2012 NICE and 2010 SIGN

guidelines recommend biologic therapies for the treatment of moderate-to-severe psoriasis owing to higher efficacy when compared with other therapies.

Table 2.5 provides a summary of adult dosing recommendations, major adverse effects regarding biologic therapies for psoriasis treatment and drug authorisation.

Table 2.5 Summary of biologic therapies for the treatment of psoriasis

	Adalimumab (Humira®)	**Etanercept (Enbrel®)**	**Infliximab (Remicade®)**	**Ustekinumab (Stelara®)**	**Secukinumab (Cosentyx®)**	**Ixekizumab (Taltz®)**
Biologic group	**TNFi**	**TNFi**	**TNFi**	**Anti-IL-12/23 agent**	**Anti-IL-17A agent**	**Anti-IL-17A agent**
Product licensed recommendation for moderate to severe chronic plaque psoriasis in adults[246]	**Initial dose**: 80 mg SC., followed by 40 mg SC. every other week	**Recommended dose**: 25 mg SC. twice weekly or 50 mg SC. once weekly. **Alternatively,** 50 mg SC. twice weekly for up to 12 weeks followed by 25 mg SC. twice weekly or 50 mg SC. once weekly.	5 mg/kg IV. repeated 2 and 6 weeks after the initial infusion, then every 8 weeks	**Initial dose**: 45 mg SC. followed by a 45 mg dose 4 weeks after the initial dose and then 45 mg every 12 weeks **Patients with body-weight over 100 kg** **Initial dose**: 90 mg followed by a 90 mg dose 4 weeks after the initial dose and then 90 mg every 12 week (45 mg dose can be used among these patients but 90 mg dose provides	**Initial dose**: 300 mg SC. at weeks 0, 1, 2 and 3 then monthly maintenance dosing starting at week 4	**Initial dose**: 160 mg SC. at weeks 0, followed by 80 mg SC. week 2, 4, 6, 8, 10 and 12 then 80 mg SC. every 4 weeks

	Adalimumab (Humira®)	Etanercept (Enbrel®)	Infliximab (Remicade®)	Ustekinumab (Stelara®)	Secukinumab (Cosentyx®)	Ixekizumab (Taltz®)
				greater efficacy.)		
Decision to continue treatment if patients do not respond[246]	At week 16	At week 12	At week 14	At week 28	At week 16	At week 12 – 16
NICE recommended dose	**Initial dose**: 80 mg SC., followed by 40 mg SC. every other week[307]	Not exceeding 25 mg SC. twice weekly[308]	5 mg/kg IV. Infusion over 2 hours repeated 2 and 6 weeks after the initial infusion, then every 8 weeks[309]	**Initial dose**: 45 mg SC. followed by a 45 mg dose 4 weeks after the initial dose and then 45 mg every 12 weeks **Patients with body-weight over 100 kg** **Initial dose**: 90 mg followed by a 90 mg dose 4 weeks after the initial dose and then 90 mg every 12 week[306]	**Initial dose**: 300 mg SC. at weeks 0, 1, 2 and 3 then monthly maintenance dosing starting at week 4[310]	**Initial dose**: 160 mg SC. at weeks 0, followed by 80 mg SC. week 2, 4, 6, 8, 10 and 12 then 80 mg SC. every 4 weeks[311]
NICE recommended criteria	1. Psoriasis condition fails to response conventional systemic therapies or psoriasis patients are	1. Psoriasis condition fails to response conventional	1. Psoriasis condition fails to response conventional		1. Psoriasis condition fails to response conventional systemic therapies or psoriasis patients are	

	Adalimumab (Humira®)	Etanercept (Enbrel®)	Infliximab (Remicade®)	Ustekinumab (Stelara®)	Secukinumab (Cosentyx®)	Ixekizumab (Taltz®)
	intolerant of or have a contradiction to the conventional systemic therapies including ciclosporin; methotrexate; and PUVA **and** 2. PASI ≥ 10 and DLQI >10[307,308]		systemic therapies or psoriasis patients are intolerant of or have a contradiction to the conventional systemic therapies including ciclosporin, methotrexate and PUVA **and** 2. PASI ≥ 20 and DLQI >18[309]	systemic therapies or psoriasis patients are intolerant of or have a contradiction to the conventional systemic therapies including ciclosporin; methotrexate; and PUVA **and** 2. PASI ≥ 10 and DLQI >10[306]	intolerant of or have a contradiction to the conventional systemic therapies including ciclosporin; methotrexate; and PUVA **and** 2. PASI ≥ 10 and DLQI >10[310,311]	
Discontinuation if patients have an inadequate response[a]	At week 16[307]	At week 12[308]	At week 10[309]	At week 16[306]	At week 12[310]	At week 12[311]
Side effects						
Main	- Infections including tuberculosis and hepatitis B reactivation, septicaemia, nausea, abdominal pain, antibody information, pruritus, injection-site reactions, blood disorders [241,312]			Nasopharyngitis, headache, upper respiratory tract infection, cutaneous and non-cutaneous malignancies [246]	Upper respiratory tract infections especially nasopharyngitis and rhinitis[246]	Injection site reactions and upper respiratory tract infections especially

	Adalimumab (Humira®)	Etanercept (Enbrel®)	Infliximab (Remicade®)	Ustekinumab (Stelara®)	Secukinumab (Cosentyx®)	Ixekizumab (Taltz®)
						nasopharyngitis [246]
CVD [246]	**Cardiac disorder** Common (≥ 1% to < 10%): Tachycardia Uncommon (≥ 0.1 to < 1%): MI, Arrhythmia Rare (≥ 0.01% to < 0.1%): Congestive heart failure **Vascular disorders** Common Hypertension, flushing, haematoma	**Cardiac disorder** Not known frequency Worsening of congestive heart failure	**Cardiac disorders** Common Tachycardia, palpitation. Uncommon Cardiac failure (new onset or worsening), arrhythmia, syncope, bradycardia. Rare: Cyanosis, pericardial effusion. Not known frequency Myocardial ischaemia/MI occurring during or within two hours of infusion.	No information	No information	No information

	Adalimumab (Humira®)	Etanercept (Enbrel®)	Infliximab (Remicade®)	Ustekinumab (Stelara®)	Secukinumab (Cosentyx®)	Ixekizumab (Taltz®)
	Uncommon Aortic aneurysm vascular arterial occlusion, thrombophlebitis		**Vascular disorders** Common Hypotension, hypertension, ecchymosis, hot flush, flushing. Uncommon Peripheral ischaemia, thrombophlebitis, haematoma. Rare Circulatory failure, petechia, vasospasm.			
Authorisation[47,246,313–315]						
In the US						
First authorisation	2002	1998	1998	2009	2015	2016
For psoriatic arthritis	2005	2002	2005	2013	2016	2017
For moderate to severe chronic plaque	2008	2004	2006	2009	2015	2016

	Adalimumab (Humira®)	Etanercept (Enbrel®)	Infliximab (Remicade®)	Ustekinumab (Stelara®)	Secukinumab (Cosentyx®)	Ixekizumab (Taltz®)
psoriasis						
In the UK						
First authorisation	2003	2000	1999	2009	2015	2016
For psoriatic arthritis	2005	2005	2004	2013	2015	2016
For moderate to severe chronic plaque psoriasis	2007	2005	2005	2009	2015	2016

Notes: [a] An adequate response is defined as either having PASI 75 from the beginning of treatment or having PASI 50 and 5-point reduction in DLQI from the beginning of treatment.

Abbreviations: CVD, Cardiovascular disease; DLQI, dermatology life quality index; IL, interleukin; IV, intravenous; MI, myocardial infarction; NICE, National Institute for Health and Care Excellence; PASI, psoriasis area and severity index; PUVA, psoralen and ultraviolet A; SC, subcutaneous; TNFi, tumour necrosis factor-alpha inhibitors

Table 2.5 Summary of biologic therapies for the treatment of psoriasis (continued)

	Brodalumab (Kyntheum® in the UK; Siliq® in the US)	**Guselkumab (Tremfya®)**	**Certolizumab (Cimzia®)**
Biologic group	**Anti-IL-17RA agent**	**Anti-IL-23 agent**	**TNFi**
Product licensed recommendation for moderate to severe chronic plaque psoriasis in adults[246]	**Initial dose**: 210 mg SC. at week 0, 1, 2 and then every 2 weeks	**Initial dose**: 100 mg SC. at week 0 and 4 followed by 100 mg SC. every 8 weeks	**Initial dose**: 400 mg SC. at week 0, 2 and 4 then maintenance dosing 200 mg every 2 weeks; or 400 mg every 2 weeks in patients with insufficient response
Decision to continue treatment if patients do not respond[246]	At week 12 - 16	At week 16	At week 16
NICE recommended dose	**Initial dose**: 210 mg SC. at week 0, 1, 2 and then every 2 week[316]	**Initial dose**: 100 mg SC. at week 0 and 4 followed by 100 mg SC. every 8 weeks[317]	Under review
NICE recommended criteria[316,317]	1. Psoriasis condition fails to response conventional systemic therapies or psoriasis patients are intolerant of or have a contradiction to the conventional systemic therapies including ciclosporin; methotrexate; and PUVA **and** 2. PASI ≥ 10 and DLQI >10		Under review
Discontinuation if patients have an inadequate response[a]	At week 12[316]	At week 16[317]	Under review

	Brodalumab (Kyntheum® in the UK; Siliq® in the US)	Guselkumab (Tremfya®)	Certolizumab (Cimzia®)
Side effects			
Main[246]	Arthralgia, headache, fatigue, diarrhoea and oropharyngeal pain	Upper respiratory infection	Infection
CVD [246]	No information	No information	**Cardiac disorders** Uncommon Cardiomyopathies (e.g. heart failure), ischaemic coronary artery disorders , arrhythmias (e.g. atrial fibrillation), palpitations Rare: Pericarditis, atrioventricular block **Vascular disorders** Common Hypertension Uncommon haemorrhage or bleeding, hypercoagulation (e.g. thrombophlebitis, pulmonary embolism), syncope, oedema (e.g.peripheral and facial),

	Brodalumab (Kyntheum® in the UK; Siliq® in the US)	Guselkumab (Tremfya®)	Certolizumab (Cimzia®)
			ecchymoses (e.g. haematoma and petechiae) Rare Cerebrovascular accident, arteriosclerosis, Raynaud's phenomenon, livedo reticularis, telangiectasia
Authorisation			
In the US[314]			
First authorisation	2017	2017	2008
For psoriatic arthritis	-	-	2013
For moderate to severe chronic plaque psoriasis	2017	2017	2018
In the UK[246]			
First authorisation	2017	2017	2009
For psoriatic arthritis	-	-	2013
For moderate to severe chronic plaque psoriasis	2017	2017	2018

2.9 Biologic therapies and cardiovascular disease

Patients with psoriasis are at high risk of developing CVD. Although the mechanism of this association remains uncertain, it is suspected that psoriasis-associated chronic inflammation may increase this risk. Therefore, psoriasis therapies (e.g. biologic therapies) which have anti-inflammatory effect may decrease the cardiovascular risk.[318] TNFi have been demonstrated to modify CRP (a cardiovascular predictor), adiponectin (having anti-inflammatory, atherogenic and anti-diabetic properties), VEGF (relating to inflammation) and resistin (relating insulin resistance).[269,319–323] These effects may result in a decreased risk of CVD. Some studies showed that TNFi provided a beneficial effect on the development of atherosclerosis and facets of metabolic syndrome.[324–327] However, some studies did not find these benefits.[272,328] Moreover, an excess mortality rate was found in psoriasis patients with severe congestive heart failure who were treated with high dose infliximab in clinical trials. This led to premature termination of these clinical trials.[329,330] In addition, another clinical trial of etanercept did not show benefit on death rate or hospitalisation owing to chronic heart failure.[331] The US Food and Drug Administration (FDA) also received 47 spontaneous reports relating to new onset or worsening heart failure in patients using infliximab or etanercept.[332] Due to these findings, the BAD recommendations in the UK on the use of TNFi in patients with psoriasis and CVD are as follows.[330]

1. Patients with New York Heart Association (NYHA) class III and IV heart failure should not be treated with TNFi.
2. Patients with NYHA class I and II heart failure should be examined and consult with a cardiology specialist before starting TNFi.
3. If patients develop a new symptom or worsening of pre-existing heart failure, they should discontinue TNFi and seek specialist advice.

Furthermore, the anti-IL-12/23 briakinumab has also been associated with an elevated risk of MACEs (MI, cerebrovascular accident or cardiovascular death). This has raised concern regarding whether IL-12/23 inhibitors as a class effect could be associated with an increased risk of CVD.[333,334] This directly led to the discontinuation of the development programme of briakinumab.[335]

Despite the concern regarding cardiovascular risk due to the use of biologic therapies in patients with psoriasis, the evidence in this area is limited. There have been earlier two meta-analyses examining the risk of MACEs and biologic therapies for the treatment of psoriasis. Nonetheless, they did not focus on current licensed biologics and dosage regimens.[336,337] Although there were studies examining the association between cardiovascular events and biologic therapies in patients with other diseases such as rheumatoid arthritis[338,339], the results of these studies could not be generalised to patients with psoriasis. Since patients with different diseases have different types or prevalence of comorbidities; or different concomitant drugs, these factors can have an influence on the assessment of the impact of biologic therapies on

CVD. Thus, systematic review and meta-analyses of RCTs which are the best study design for answering this unclear association are needed.

However, patients in RCTs tend to be different from patients in real-life practice. For example, they are often healthier having fewer comorbidities than patients in real-life practice. Moreover, the durations of the trials often mean that patients are treated for shorter periods than most patients in clinical practice who may receive treatments for much longer periods of time. Thus, it requires prospective cohort studies examining the impact of biologic therapies on major CVEs among patients with psoriasis which take into account of some of the limitations of RCTs as well.

There were earlier cohort studies assessing the association between CVEs and biologic therapies in patients with psoriasis. Nevertheless, these studies have important limitations. These studies used unsuitable reference groups which were non-biologic therapies, non-systemic therapies (topical therapy, phototherapy and climate therapy) or methotrexate.[7–11] These therapies are typically recommended for patients before receiving biologic therapies. Thus, they tend to be used in patients with milder severity of psoriasis compared with patients receiving biologic therapies. To assess the association between CVEs and treatments, participants in treatment and reference groups should have similar severity of psoriasis since this can influence the development of CVEs.[220] Ideally, biologic therapies should be directly compared. Databases used for this assessment should contain detailed information including the severity of psoriasis. The BADBIR is a prospective cohort study which has collected information from patients with psoriasis treated with biologic therapies or conventional systemic therapies alone across the UK and Republic of Ireland.[12] It contains detailed information on treatment exposures, the severity of psoriasis, comorbidities, adverse events (AEs) etc. Therefore, it is an excellent resource for examining the impact of biologic therapies on major CVEs in patients with psoriasis.

2.10 Rationale for the work presented in this thesis

As mentioned above, psoriasis is recognised as an important disease due to its negative impact on patients' physical, mental and social life.[14,15] The WHO has recognised and encouraged each country to pay attention and take care of patients with psoriasis.[16] The available evidence suggests that patients with psoriasis are at high risk of a number of comorbidities such as CVD, hypertension and diabetes. Some of these comorbidities (e.g. diabetes) are serious and are also a major global concern. Moreover, deleterious lifestyle habits including cigarette smoking and alcohol consumption which are common in patients with psoriasis can contribute to an increased risk of some comorbidities. Recognition of comorbidities and lifestyle habits is crucial for optimising management and monitoring for patients with psoriasis.

To explore this in more detail requires a large database containing detailed information that has been collected in a standardised way. The UK Biobank is a large database which has collected information about 500,000 participants in the UK.[6] Specifically, this includes information on participants' medical history, lifestyle, and physical measures. It is also linked to National Health Service (NHS) hospital episode statistics, mortality and cancer registrations. Thus, it is an excellent source to measure the prevalence and the associations of comorbidities associated with psoriasis. A cross-sectional study design can be used to examine the prevalence of comorbidities.

Cardiovascular comorbidities have been reported as being common among patients with psoriasis.[115] Several observational studies have suggested that patients with severe psoriasis and psoriatic arthritis have a higher risk of CVEs such as MI, stroke and cardiovascular death.[107,154,221,340] It is debated whether this represents a causal association or a predisposition due to the underlying risk factors exhibited by patients with severe psoriasis[341–343], but there is a hypothesis postulating that the inflammatory cascade activated in patients with severe psoriasis may contribute to the development of atherosclerosis.[344] Moreover, cardiovascular risk factor screening of adult patients with psoriasis in primary care has found a high proportion of patients being sub-optimally treated for known cardiovascular risk factors.[345] All these factors can contribute to an increased risk of CVEs in patients with psoriasis. Thus, medications for psoriasis, such as biologic therapies, which have anti-inflammatory effects could theoretically improve atherosclerosis, and therefore modulate the risk of development of CVD.[226,346–349]

Biologic therapies for the treatment of moderate-severe plaque psoriasis included TNFi (infliximab, etanercept and adalimumab); an anti-IL-12/23 agent (ustekinumab); and anti-IL-17A agents (secukinumab and ixekizumab) which were approved by the US FDA, the European Medicine Agency (EMA) or any European country at the time this thesis prepared. These therapies have been increasingly used over the last decade owing to higher efficacy compared to other psoriasis treatments. It is currently unclear whether any of these therapies could alter the risk of development of CVD. However, a number of MACEs (MI, cerebrovascular accident, or cardiovascular death) were observed in psoriasis patients receiving briakinumab, another IL-12/23 inhibitor, in RCTs, and this has raised concern regarding whether IL-12/23 inhibitors could be associated with an increased risk of CVD.[333,350] This directly led to the discontinuation of the development programme of briakinumab.[335] Despite the approval and licensing of several biologic therapies for the treatment of psoriasis by the regulatory agencies for more than 10 years, the cardiovascular safety profile of these medicines is not well established.

There has not been a systematic review and meta-analysis examining the impact of all of these medicines on the risk of MACEs. There are studies examining the association between CVEs and biologic therapies in patients with other diseases such as rheumatoid arthritis[338,339], but the results of these studies could not be generalised to patients with psoriasis. Since patients with different diseases have different types or prevalence of comorbidities; or different concomitant

drugs, these factors can have an influence on the assessment of the impact of biologic therapies on the risk of MACEs. Thus, there is a need to assess the association between the risk of MACEs due to the use of biologic therapies in patients with psoriasis.

Systematic review and meta-analysis are considered as the highest hierarchy of evidence-based practice while RCT is the strongest study design to test hypotheses and make firm causal conclusions.[351,352] Thus, systematic review and meta-analysis of RCTs are a robust way to examine the association between MACEs and biologic therapies in patients with psoriasis during the follow-up of the trials. Therefore, this study design will be used to explore this relationship.

Patients' characteristics in clinical practice tend to be different from those participating in RCTs as they often have more comorbidities. Therefore, larger scale prospective observational studies are also important in evaluating the association between CVEs and biologic therapies in clinical practice. Previous cohort studies examining the impact of biologic therapies on CVEs in patients with psoriasis had some important limitations such as using inappropriate reference groups and insufficiently controlling for cardiovascular confounders. Thus, well-designed prospective cohort studies assessing this association in patients with psoriasis are needed. The BADBIR is a large prospective cohort study which has collected clinical information among patients with psoriasis treated with biologic therapies or conventional systemic therapies from secondary care dermatology centres across the UK and Republic of Ireland.[12] It has collected detailed information on comorbidities, the severity of psoriasis, use of drug therapies, AEs etc. Moreover, it is also linked with the Office of National Statistics (ONS) mortality dataset. Therefore, it is an excellent resource from which to examine the association between major CVEs and biologic therapies among patients with psoriasis in clinical practice. Both the results from the systematic review and meta-analysis and the prospective cohort study will help to inform whether biologic therapies have any impact on the risk of CVE.

Chapter 3

Aims and objectives

3.1 Aims

The broad aims of this thesis were to examine the prevalence of physical and mental health comorbidities in patients with psoriasis and then subsequently examine the impact of biologic therapies on the risk of CVEs in patients with psoriasis. Participants registered with the UK Biobank were used to examine comorbidities of psoriasis. The association between biologic therapies and CVEs in patients with psoriasis was assessed by using a systematic review and meta-analysis of RCTs and data from the BADBIR which is a large prospective cohort study.

3.2 Specific study objectives

To achieve the aims of this thesis, three empirical studies were conducted. They included a cross-sectional study using the UK Biobank (Chapter 4), a systematic review and meta-analysis of RCTs (Chapter 5) and a prospective cohort study in the BADBIR (Chapter 6). The objectives of these studies were as follows.

- To quantify prevalence rates of physical and mental health comorbidities in patients with psoriasis and compare them with participants without psoriasis using a cross-sectional study of the UK Biobank
- To calculate prevalence ratios (PRs) of comorbidities in patients with psoriasis compared with participants without psoriasis using a cross-sectional study of the UK Biobank
- To calculate ORs for the different numbers of comorbidities in patients with psoriasis compared participants without psoriasis using a cross-sectional study of the UK Biobank
- To examine the association between biologic therapies and MACEs in adult patients with plaque psoriasis by conducting a systematic review and meta-analysis of RCTs
- To examine the incidence rates, incidence rate ratios and HRs for the risk of major CVEs in adults with plaque psoriasis treated with biologic therapies or methotrexate using a prospective cohort study in the BADBIR

Chapter 4

Examining the demographic and anthropometric characteristics of patients with psoriasis and prevalence of physical and mental health comorbidities: cross-sectional study of the UK Biobank

4.1 Introduction

As described in Chapter 2, many published studies have examined the prevalence of specific comorbidities in patients with psoriasis, but very few have reported on the burden of both physical and mental health comorbidities. In order to investigate this further to better inform clinical practice, large patient cohorts are required containing detailed information on patients demographic, anthropometric and disease characteristics. The UK biobank has collected clinical information and lifestyle habits from over 500,000 middle-to-old aged participants across the UK. This age group is likely to develop the most common and serious comorbidities such as CVD and hypertension. Therefore, the UK Biobank is an important resource which can be used to characterise the detailed comorbid conditions of patients with psoriasis. This chapter describes the UK Biobank and the results of a cross-sectional study examining the prevalence of both physical and mental health comorbidities in participants with and without psoriasis included in the UK Biobank dataset. This study was conducted using the UK Biobank resources under application number 34728.

4.2 Aim and objectives

This study aimed to assess the demographic and anthropometric characteristics of patients with psoriasis and the prevalence of physical and mental health comorbidities or lifestyle habits in a cross-sectional analysis of the UK Biobank.

The objectives of this study were:

- To compare demographic and anthropometric characteristics including lifestyle habits of participants with and without psoriasis
- To calculate the prevalence rates and the PRs for specific physical and mental health comorbidities in participants with psoriasis when compared with participants without psoriasis
- To compare the numbers of comorbidities and calculate PRs and ORs for participants with psoriasis compared with participants without psoriasis

4.3 Methods

4.3.1 UK Biobank Database

The UK Biobank is a large prospective cohort and is one of the largest biobank databases in the world. This database aims to support a diverse range of research so as to improve the prevention, diagnosis and treatment of serious and life-threatening diseases among middle and old aged people.[353] The UK Biobank researchers sent postal investigation to 9,238,453 middle-to-old aged individuals who registered with the UK NHS and lived within about 25 miles of one of 22 assessment centres across the UK.[354] Overall, 502,616 male and female participants, aged 37 - 73 years consented to join this study cohort and visited an assessment centre during

2006 – 2010.[355] The ethical approval for the UK Biobank was obtained from the Norths West Multi-centre Research Ethics Committee (reference number 16/NW/0274) (Appendix 1). Participants who have participated in this study had to read the information leaflet and signed the consent form (Appendix 2 and 3).

4.3.2 Data collection

Each participant had to complete a touch-screen questionnaire, nurse-led interview and physical measurement at the assessment centres to collect baseline information. The touch-screen questionnaire was used to collect information on sociodemographic characteristics (e.g. ethnicity and postcode of residence which was used to calculate Townsend score indicating socioeconomic deprivation). These scores were subsequently categorised into socioeconomic deprivation quintiles. Moreover, the questionnaire also obtained information on lifestyle behaviours (e.g. smoking, a frequency of alcohol consumption and physical activity) and medical conditions. Physical activity was also based on self-report and categorised into four groups:1) high (strenuous sports in the last 4 weeks), 2) medium [heavy do-it-yourself (DIY) e.g. weeding, lawn mowing, carpentry, digging; and/or walking for pleasure (not as a means of transport); and/or other exercises e.g. swimming, cycling keep fit, bowling in the last 4 weeks], 3) low (4=light DIY e.g. pruning, watering the lawn in the last 4 weeks) and 4) none (no physical activity in the last 4 weeks). Participants reported their frequency of alcohol consumption as daily or almost daily, 3 - 4 times/week, 1 - 2 times/week, 1 - 3 times/month, special occasions only and never. Smoking status consisted of the following categories: current, previous or never smoker. Participants self-reported their medical conditions to the interviewers (trained nurses). Furthermore, physical examinations (e.g. weight and height to calculate BMI) were measured. The UK Biobank started linking to NHS hospital episode statistics, mortality and cancer registrations during 2013 – 2015 in order to collect previous and current health-related outcomes for all participants.[355] However, only comorbidities self-reported at baseline were analysed for the current study.

4.3.3 Study design

A cross-sectional study was used to compare the demographic and anthropometric characteristics and physical and mental health comorbidities of participants with psoriasis to those without this disease in the UK Biobank.

Defining study population; and physical and mental health comorbidities

Participants with and without psoriasis enrolled in the UK Biobank were compared. The psoriasis group included patients reporting psoriasis and/or psoriatic arthritis while the no psoriasis group included participant without these diseases. Psoriasis and/or psoriatic arthritis were defined as self-report of the conditions by the nurse-led interview. The lists of physical and mental health comorbidities in this study (Appendix 4) were adapted from a long-term

comorbidity list which was originally established for a large Scottish epidemiological study.[356] This Scottish study considered results from a systematic review studying multimorbidity in papers published during 1960 - 2009, diseases in the quality and outcomes framework of the UK general practice contract and long-term conditions defined as important by the NHS Scotland and an expert panel.[356] The list was then amended for the UK Biobank.[357]

Data analyses

Participants with and without psoriasis were compared regarding their sociodemographic, lifestyle and presence of physical and mental health comorbidities. The proportion (%) and median [25th percentile (p25) - 75th percentile (p75)] were calculated for categorical and continuous variables, respectively. The prevalence rates were estimated and represented percentages for both groups. The crude and age, sex and socioeconomic deprivation adjusted PRs of physical and mental health comorbidities and the numbers of these comorbidities with 95% CIs were calculated comparing participants with and without psoriasis. PRs were estimated using log-binomial regression models. A multinomial logistic regression model was used to examine the association between the numbers of comorbidities overall, and then separately for both physical and mental health comorbidities and psoriasis. Results were presented as ORs adjusted for age, sex and deprivation with 95% CIs.

All analyses were performed using Stata 15 (StataCorp LP, College Station, Texas, USA).

4.4 Results

Of the 502,543 participants, 6,105 (1.21%) had psoriasis, as shown in Table 4.1. Participants with and without psoriasis had the same median age (58 years) and the vast majority of them were white (96.5% vs 94.1%). Men were over-represented in the psoriasis group (52.4%) while 45.5% of the no psoriasis group were men. A slightly higher proportion of participants with psoriasis resided in the most deprived quintile compared to those without psoriasis (22.8% vs 20.0%). Patients with psoriasis were more likely to be obese (30.1% vs 24.4%), smoke (56.2% vs 44.9%) and less likely to engage in physical activity (9% vs 6.5%). Both groups had a similar frequency of alcohol consumption.

Table 4.1 Baseline characteristics of the UK Biobank study population comparing participants with and without psoriasis

Characteristics	Psoriasis N=6,105 n (prevalence rate %)	No psoriasis N=496,438 n (prevalence rate %)
Age (years) (median, p25-p75)	**58 (50 - 63)**	**58 (50 - 63)**
Sex, male (N=502,543)	**3,198 (52.4)**	**225,940 (45.5)**
Ethnicity		
White	5,894 (96.5)	466,892 (94.1)
Mixed race	29 (0.5)	2,930 (0.6)
South and other Asian	98 (1.6)	9,785 (2.0)
Black	16 (0.3)	8,048 (1.6)
Chinese	5 (0.1)	1,569 (0.3)
Other	33 (0.5)	4,527 (0.9)
Missing	30 (0.5)	2,687 (0.5)
Deprivation quintile (N=501,920)	**N=6,101**	**N=495,819**
1 (least deprived)	1,134 (18.6)	99,530 (20.1)
2	1,145 (18.8)	98,961 (20.0)
3	1,1990 (19.7)	99,191 (20.0)
4	1,233 (20.2)	99,145 (20.0)
5 (most deprived)	1,390 (22.8)	98,992 (20.0)
BMI (kg/m^2) (median, p25-p75)	**27.6 (24.8 – 30.9)**	**26.7 (24.1 – 29.9)**
BMI classification (kg/m^2)		
Underweight (< 18.5)	27 (0.4)	2,599 (0.5)
Normal (18.5 – 24.9)	1,595 (26.1)	160,830 (32.4)
Overweight (25.0 – 29.9)	2,625 (43.0)	209,504 (42.2)
Obesity Class I (30.0-34.9)	1,219 (20.0)	86,340 (17.4)
Obesity Class II (35.0–39.9)	424 (7.0)	24,571 (5.0)
Obesity class III (≥ 40.0)	187 (3.1)	9,517 (1.9)
Missing	28 (0.5)	3,077 (0.6)
Obesity (BMI≥30kg/m^2) (%)	**1,830 (30.1)** **n= 6,077**	**120,428 (24.4)** **n= 493,361**
Physical activity (median, p25 – p75)		
High	502 (8.2)	49,570 (10.0)
Medium	4,738 (77.6)	388,788 (78.3)
Low	265 (4.3)	18,675 (3.8)
None	550 (9.0)	32,299 (6.5)
Missing	50 (0.8)	7,106 (1.4)
Smoking status		
Current	934 (15.3)	52,045 (10.5)

Characteristics	Psoriasis N=6,105 n (prevalence rate %)	No psoriasis N=496,438 n (prevalence rate %)
Ex	2,499 (40.9)	170,573 (34.4)
Never	2,645 (43.3)	270,897 (54.6)
Missing	27 (0.4)	2,923 (0.6)
Alcohol consumption		
Daily/almost daily	1,290 (21.1)	100,485 (20.2)
3 - 4 times/week	1,391 (22.8)	114,055 (23.0)
1 - 2 times/week	1,492 (24.5)	127,806 (25.7)
1 – 3 times/month	686 (11.2)	55,174 (11.1)
Special occasions only	717 (11.7)	57,296 (11.5)
Never	514 (8.4)	40,135 (8.1)
Missing	15 (0.3)	1,487 (0.3)

Abbreviations: BMI, body mass index; p25-p75, 25th percentile - 75th percentile

Physical comorbidities

The no psoriasis group had a higher proportion of individuals with no physical or mental health illnesses than patients with psoriasis. Crude and age, sex and deprivation adjusted PRs of CVD and cardiovascular risk factors including hypertension, history of MI, peripheral vascular disease, high cholesterol, diabetes, psoriatic arthritis or rheumatoid arthritis were significantly higher in patients with psoriasis compared to participants without psoriasis, as shown in Table 4.2. Patients with psoriasis were far more likely to have a diagnosis of inflammatory arthritis (psoriatic arthritis or rheumatoid arthritis) than participants without psoriasis (prevalence rates: 16.9% vs 1.1% and the crude and adjusted PR [15.16 (95% CI 14.25 – 16.12) and 15.10 (95% CI 14.22 – 16.05)]. The prevalence rates for heart failure/pulmonary oedema; and previous stroke or transient ischemic attack were very low for both groups and the crude and age, sex and deprivation adjusted PRs for these diseases were not significantly different among both groups.

Moreover, osteoarthritis (11% vs 8.1%), gout (2% vs 1.4%), inflammatory bowel disease (1.5% vs 0.8%), irritable bowel syndrome (3.2% vs 2.3%), cirrhosis/liver failure including alcoholic liver disease/alcoholic cirrhosis (0.3% vs 0.1%), renal failure (0.3% vs 0.2%) and migraine (3.2% vs 2.9%) were significantly more prevalent in those with psoriasis relative to those without psoriasis. The adjusted PRs for these diseases ranged from 1.19 – 1.82 except for cirrhosis/liver failure including alcoholic liver disease/alcoholic cirrhosis (2.86). The prevalence rates for skin cancer, including malignant and non-malignant melanoma for both groups were very low and the crude and adjusted PRs showed no significant differences.

Table 4.2 Prevalence rates and prevalence ratios for physical comorbidities

Comorbidity	Psoriasis n=6,105 n (prevalence rate %)	No psoriasis n=496,438 n (prevalence rate %)	Crude PR (95% CI) (psoriasis vs no psoriasis)	PR adjusted for age, sex and deprivation (95% CI) (psoriasis vs no psoriasis)
No comorbidity	1,055 (17.3)	121,738 (24.5)	0.71 (0.67 – 0.75)	0.71 (0.67 – 0.75)
Cardiovascular disease				
Hypertension	1,876 (30.7)	132,785 (26.8)	1.15 (1.11 – 1.19)	1.13 (1.09 – 1.17)
Previous heart attack/MI	179 (2.9)	11,326 (2.3)	1.29 (1.11 – 1.49)	1.17 (1.01 – 1.35)
Heart failure/pulmonary oedema	5 (0.1)	310 (0.1)	1.31 (0.54 – 3.17)	1.23 (0.51 – 2.98)
Atrial fibrillation	54 (0.9)	3,597 (0.7)	1.22 (0.93 – 1.60)	1.17 (0.90 – 1.53)
Previous stroke or transient ischaemic attack	111 (1.8)	8,741 (1.8)	1.03 (0.86 – 1.24)	0.99 (0.82 – 1.19)
Peripheral vascular disease	28 (0.5)	1,423 (0.3)	1.60 (1.10 – 2.32)	1.56 (1.08 – 2.27)
Previous venous thromboembolic disease	166 (2.7)	12,588 (2.5)	1.07 (0.92 – 1.25)	1.08 (0.93 – 1.26)
High cholesterol	845 (13.8)	60,790 (12.3)	1.13 (1.06 – 1.20)	1.10 (1.03 – 1.17)
Respiratory disease				
Asthma	675 (11.1)	57,605 (11.6)	0.95 (0.89 – 1.02)	0.96 (0.89 – 1.03)
Chronic obstructive airways disease/COPD	24 (0.4)	1,642 (0.3)	1.19 (0.79 – 1.78)	1.15 (0.77 – 1.72)
Chronic sinusitis	51 (0.8)	3,051 (0.6)	1.36 (1.03 – 1.79)	1.38 (1.05 – 1.82)

Comorbidity	Psoriasis n=6,105 n (prevalence rate %)	No psoriasis n=496,438 n (prevalence rate %)	Crude PR (95% CI) (psoriasis vs no psoriasis)	PR adjusted for age, sex and deprivation (95% CI) (psoriasis vs no psoriasis)
Gastrointestinal/abdominal disorders				
Inflammatory bowel disease	92 (1.5)	4,139 (0.8)	1.81 (1.47 – 2.22)	1.82 (1.48 – 2.23)
Irritable bowel syndrome	198 (3.2)	11,294 (2.3)	1.43 (1.24 – 1.64)	1.51 (1.32 – 1.73)
Diverticular disease/diverticulitis	104 (1.7)	5,298 (1.1)	1.60 (1.32 – 1.93)	1.67 (1.38 – 2.02)
Cirrhosis/liver failure including alcoholic liver disease/alcoholic cirrhosis	18 (0.3)	494 (0.1)	2.96 (1.85 – 4.74)	2.86 (1.79 – 4.58)
Renal failure	**20 (0.3)**	**864 (0.2)**	**1.88 (1.21 – 2.93)**	**1.81 (1.16 – 2.82)**
Endocrine disorder				
Diabetes	417 (6.8)	25,327 (5.1)	1.34 (1.22 – 1.47)	1.26 (1.15 – 1.38)
Thyroid problem	348 (5.7)	28,811 (5.8)	0.98 (0.89 – 1.09)	1.08 (0.98 – 1.19)
Neurology/eye disorder				
Multiple sclerosis	19 (0.3)	1,758 (0.4)	0.88 (0.56 – 1.38)	0.93 (0.59 – 1.46)
Epilepsy	41 (0.7)	4,013 (0.8)	0.83 (0.61 – 1.13)	0.81 (0.59 – 1.10)
Migraine	193 (3.2)	14,192 (2.9)	1.11 (0.96 – 1.27)	1.19 (1.03 – 1.36)
Glaucoma	76 (1.2)	5,238 (1.1)	1.18 (0.94 – 1.48)	1.17 (0.94 – 1.47)
Cataract	99 (1.6)	7,215 (1.5)	1.12 (0.92 – 1.36)	1.13 (0.93 – 1.38)

Comorbidity	Psoriasis n=6,105 n (prevalence rate %)	No psoriasis n=496,438 n (prevalence rate %)	Crude PR (95% CI) (psoriasis vs no psoriasis)	PR adjusted for age, sex and deprivation (95% CI) (psoriasis vs no psoriasis)
Musculoskeletal disease				
Rheumatoid arthritis or psoriatic arthritis	1,031 (16.9)	5,532 (1.1)	15.16 (14.25 – 16.12)	15.10 (14.22 – 16.05)
Osteoarthritis	669 (11.0)	40,022 (8.1)	1.36 (1.26 – 1.46)	1.40 (1.30 – 1.50)
Gout	124 (2.0)	6,855 (1.4)	1.47 (1.23 – 1.75)	1.30 (1.10 – 1.55)
Cancer				
Any cancers	459 (7.5)	40,786 (8.2)	0.92 (0.84 – 1.00)	0.95 (0.87 – 1.04)
Skin cancer	142 (2.3)	11,119 (2.2)	1.04 (0.88 – 1.22)	1.07 (0.91 – 1.25)
Malignant melanoma	44 (0.7)	3,665 (0.7)	0.98 (0.73 – 1.31)	1.01 (0.75 – 1.36)
Non-malignant melanoma	80 (1.3)	6,145 (1.2)	1.06 (0.85 – 1.32)	1.09 (0.88 – 1.36)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PR, prevalence ratio

Mental health comorbidities

Table 4.3 shows that the prevalence rates for almost specific mental health comorbidities which were found to be significantly higher in the psoriasis group than the no psoriasis group (7.7% vs 5.6% for depression, 1.9% vs 1.3% for anxiety/panic attacks, 0.4% vs 0.2% for alcohol dependency and 0.7% vs 0.4% for schizophrenia or mania/bipolar disorder/manic depression. The adjusted PRs for these comorbidities ranged from 1.38 – 1.73 except for alcohol dependency (2.18).

Table 4.3 Prevalence rates and prevalence ratios for mental health comorbidities

Comorbidity	Psoriasis n=6,107 n (prevalence rate %)	No psoriasis n=496,509 n (prevalence rate %)	Crude PR (95% CI) (psoriasis vs no psoriasis)	PR adjusted for age, sex and deprivation (95% CI) (psoriasis vs no psoriasis)
Depression	467 (7.7)	28,006 (5.6)	1.36 (1.24 – 1.48)	1.38 (1.26 – 1.51)
Anxiety/panic attacks	116 (1.9)	6,608 (1.3)	1.43 (1.19 – 1.71)	1.45 (1.21 – 1.74)
Alcohol dependency	22 (0.4)	723 (0.2)	2.47 (1.62 – 3.78)	2.18 (1.43 – 3.33)
Schizophrenia or mania/bipolar disorder/manic depression	44 (0.7)	1,951 (0.4)	1.83 (1.36 – 2.47)	1.73 (1.29 – 2.33)
Anorexia/bulimia/other eating disorder	6 (0.1)	364 (0.1)	1.34 (0.60 – 3.00)	1.46 (0.65 – 3.27)

Abbreviations: CI, confidence interval; PR, prevalence ratio

Prevalence rates and prevalence ratios for the numbers and types of comorbidities

Overall, 30.9% of participants with psoriasis had no physical and mental health comorbidities compared with 39.7% those without psoriasis [PR 0.78 (95% CI 0.75 – 0.81)] (Table 4.4). Participants without psoriasis were more likely to have one comorbidity [PR 0.94 (95% CI 0.90 – 0.98)] while patients with psoriasis were likely to have at least two comorbidities. Psoriasis was significantly associated with the increasing numbers of overall comorbidities when compared with the no psoriasis group (Figure 4.1).

Restricting the analysis only to physical comorbidities, a similar trend was found. For mental health comorbidities, 9.8% of participants with psoriasis had at least one mental health problems relative to 7.1% of those without psoriasis. The PRs for one and at least two mental health comorbidities were 1.35 (95% CI 1.25 – 1.47) and 1.83 (95% CI 1.40 – 2.38), respectively. Psoriasis was significantly associated with the increasing numbers of mental health comorbidities when compared with the no psoriasis group.

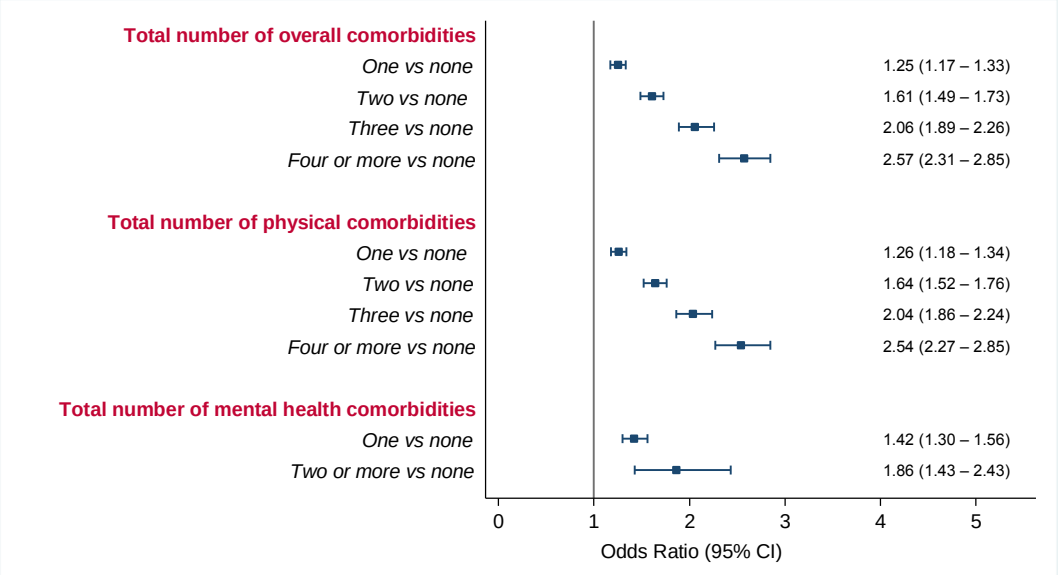
Table 4.4 Prevalence rates and prevalence ratios for the numbers and types of comorbidities

	Psoriasis n=6,105 n (prevalence rate %)	No psoriasis n=496,438 n (prevalence rate %)	Crude PR (95% CI) (psoriasis vs no psoriasis)
Total number of comorbidities[a]			
None	1,887 (30.9)	196,962 (39.7)	0.78 (0.75 – 0.81)
One	1,796 (29.4)	155,218 (31.3)	0.94 (0.90 – 0.98)
Two	1,238 (20.3)	84,988 (17.1)	1.18 (1.13 – 1.25)
Three	709 (11.6)	38,4057 (7.7)	1.50 (1.40 – 1.61)
Four or more	475 (7.8)	20,865 (4.2)	1.85 (1.70 – 2.02)
Total number of physical health comorbidities[b]			
None	2,032 (33.3)	208,823 (42.1)	0.79 (0.76 – 0.82)
One	1,834 (30.0)	155,073 (31.2)	0.96 (0.93 – 1.00)
Two	1,209 (19.8)	80,680 (16.3)	1.22 (1.16 – 1.28)
Three	645 (10.6)	34,927 (7.0)	1.50 (1.40 – 1.62)
Four or more	385 (6.3)	16,935 (3.4)	1.85 (1.68 – 2.04)
Total number of mental health comorbidities			
None	5,507 (90.2)	461,394 (92.9)	0.97 (0.96 – 0.98)
One	542 (8.9)	32,554 (6.6)	1.35 (1.25 – 1.47)
Two or more	56 (0.9)	2,490 (0.5)	1.83 (1.40 – 2.38)

Notes: [a] Excluding psoriasis and including all physical and mental health comorbidities; [b] Excluding psoriasis

Abbreviations: CI, confidence interval; PR, prevalence ratio

Figure 4.1 Odds ratios adjusted for age, sex and deprivation (95% confidence interval) comparing participants with and without psoriasis for the numbers and types of comorbidities



Abbreviation: CI, confidence interval

4.5 Discussion

This is the first cross-sectional study reporting baseline characteristics of the psoriasis population compared with no psoriasis population using the UK Biobank database. This large cross-sectional study showed that patients with psoriasis were associated with an increased prevalence of physical and mental health comorbidities and decreased prevalence of no comorbidity compared with participants without psoriasis. The results demonstrated that psoriasis was significantly related to a higher level of physical comorbidities including cardiovascular risk factors e.g. hypertension, high cholesterol and diabetes (15/30) and mental comorbidities (4/5). In addition, the numbers of overall, physical and mental health comorbidities were associated with psoriasis compared with no psoriasis. Furthermore, patients with psoriasis were more likely to have deleterious lifestyle habits such as smoking and report no physical activity.

The prevalence rates of inflammatory arthritis showed the largest difference between the psoriasis group and the no psoriasis group. Furthermore, the other musculoskeletal diseases including osteoarthritis and gout also showed elevated PRs. Rheumatoid arthritis, osteoarthritis and gout are common misdiagnoses of psoriatic arthritis.[81,358,359]

Several elevated associations between psoriasis and cardiovascular risk factors which included hypertension, high cholesterol and diabetes were found. Moreover, obesity and smoking were more prevalent in patients with psoriasis. These findings were consistent with previous studies

as reported in Chapter 2.[115,185] For CVEs, this study found that a history of MI was significantly more likely to be presented in those with psoriasis. This finding was consistent with a UK cross-sectional study using electronic medical records database [The Health Improvement Network (THIN)].[220] This association might be because of shared inflammatory pathways between psoriasis and atherosclerosis and the expression of proinflammatory cytokines.[197,360] Nevertheless, a higher prevalence of stroke or transient ischemic attack was not observed in this study. It was also not present in earlier UK and Taiwanese cross-sectional studies.[124,141]

The frequency of alcohol consumption was similar in both groups. However, alcohol dependency was more prevent in patients with psoriasis compared with those without psoriasis (0.4% vs 0.2%). This resulted in an increased risk of this condition in patients with psoriasis [crude PR 2.47 (95% CI 1.62 – 3.78) and adjusted PR 2.18 (95% CI 1.43 – 3.33)]. A recent UK cohort study using electronic health and mortality records also found that psoriasis patients had a greater risk of alcohol-related mortality compared with patients without psoriasis.[361] Thus, lifestyle modification is needed for patients with psoriasis.

Moreover, psoriasis was also found to be associated with a higher likelihood of having inflammatory bowel disease as suggested in previous studies.[91–93,95] This study did not find the relationship between psoriasis and malignant melanoma and this finding, which was consistent with a published systematic review by Pouplard et.al. 2013.[99] A higher prevalence of mental health problems was also found in those with psoriasis in this study like in previous studies.[59] However, a recent UK cohort study reported that patients with psoriasis had a lower risk of overall suicide despite of a higher prevalence of mental illness.[362] This lower risk of suicide and higher burden of mental illness might be owing to closer monitoring by clinicians in primary care.[362]

It can be seen that patients with psoriasis are more likely to have higher levels of some CVEs and cardiovascular risk factors e.g. hypertension, diabetes and smoking. It has been suggested that biologic therapies which have an increasing role in the treatment of moderate-to-severe psoriasis may alter the risk of CVEs. The next chapter will present the results of a systematic review and meta-analysis of RCTs examining whether or not this may be the case.

Chapter 5

Examining the association between major adverse cardiovascular events and biologic therapies in adult patients with psoriasis: systematic review and meta-analysis

5.1 Introduction

As highlighted in Chapter 2, several observational studies have suggested that patients with severe psoriasis and psoriatic arthritis have a higher risk of CVEs such as MI, stroke and cardiovascular death.[107,154,221,340] However, some earlier studies did not find this increased risk of CVEs. In addition, Chapter 4 of this thesis also showed that patients with psoriasis were more likely to have established CVD and cardiovascular risk factors.

Inflammation supports a theoretical association between psoriasis and CVD.[84] Thus, an inflammatory cascade activated in patients with severe psoriasis may contribute to the development of atherosclerosis. Biologic therapies which have anti-inflammatory effects may potentially reduce atherosclerosis and therefore modulate the risk of development of CVD.[226,346–349] Licensed biologic therapies for the treatment of moderate-severe plaque psoriasis approved by the US FDA, the EMA or any European county consisted of TNFi (adalimumab, etanercept and infliximab), anti-IL-12/23 agent (ustekinumab) and anti-IL-17A agents (secukinumab and ixekinumab) at the time this study was completed in 2016. Although several biologic therapies have been approved for over 10 years, the cardiovascular safety profile of these therapies is still unclear.

This chapter presents the results of a systematic review and meta-analysis of RCTs to examine the risk of MACEs in adult patients with plaque psoriasis exposed to biologic therapies.

5.2 Aim and objectives

This chapter aimed to examine the association between biologic therapies and MACEs in adult patients with plaque psoriasis. A systematic review and meta-analysis of RCTs was conducted to assess this association.

The objectives of this study were:

- To calculate combined ORs and risk differences for the risk of MACEs in patients with plaque psoriasis receiving biologic therapies from a systematic review and meta-analysis of RCTs
- To examine quality and potential publication bias of included RCTs papers from a systematic review and meta-analysis of RCTs

5.3 Methods

A systematic review and meta-analysis was conducted and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[363]

5.3.1 Eligibility criteria

RCTs reporting AEs in adult patients with plaque psoriasis receiving at least one licensed dose of biologic therapy compared with conventional systematic therapy or placebo/no treatment during the randomised controlled phase were included. The doses of biologic therapies and conventional systemic therapies assigned had to be approved by the US FDA, the EMA or any European country.

The outcomes of interest were MACEs [MI, cerebrovascular accident (including ischaemic and haemorrhagic strokes), or cardiovascular death].

5.3.2 Data sources and search strategy

The Cochrane Library, MEDLINE and Embase were independently searched without language restrictions from their inception dates to 31 March 2016. The search term sets which consisted of psoriasis, biologic therapies (individual drug names, trade names and drug classes) and study design were tailored for each database. Search strategies from MEDLINE, Embase and Cochrane are provided in the Appendix 5. MEDLINE and Embase databases were searched using all search term sets while the Cochrane Library was searched using only search term sets covering psoriasis and biologic therapies. The Cochrane handbook for systematic reviews of interventions recommends that study design should not be used as a search term set to identify RCTs in the Cochrane Library (unlike MEDLINE or Embase).[364] Both MeSH and free text terms were used to identify relevant trials.

In addition, the US FDA, EMA, five trial registries [the US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov), the EU Clinical Trials Register (www.clinicaltrialsregister.eu/), the WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/), the Australian and New Zealand Clinical Trials Registry (www.anzctr.org.au), the International Standard Randomised Controlled Trial Number (ISRCTN) registry (www.isrctn.com)], and pharmaceutical company websites [AbbVie marketing Humira® (adalimumab), Pfizer marketing Enbrel® (etanercept), Janssen and Merck marketing Remicade® (infliximab), Janssen marketing Stelara® (ustekinumab), Eli Lilly and Company marketing Taltz® (ixekizumab), and Novartis Pharmaceutical Corporation marketing Cosentyx® (secukinumab)] were searched for additional details of clinical trials. Furthermore, the reference lists of all included studies were screened to determine whether they mentioned any other eligible trials.

5.3.3 Study process

All abstracts and full-text articles were read by me (W.R.) in order to screen for the relevant trials. I and a researcher (Z.Z.N.Y.) extracted information from eligible the RCTs independently.

My supervisors (D.M.A., C.E.M.G., and R.B.W.) provided advice on the included studies in case any decision was unclear.

5.3.4 Data extraction and quality assessment

Data relating to the relevant trial comparisons (biologic therapies, conventional systemic therapies, placebo or no treatment) were extracted along with information on study characteristics [number of study sites, blinding, length of the randomised controlled phase and rate of missing patient data (defined as percentage of patients withdrawing during the study period or excluded from the analysis)]; patient characteristics (age, sex, history of psoriatic arthritis, weight, duration of psoriasis, PASI score, and percentage of BSA by psoriasis); and the numbers of participants receiving at least one dose of study drug/placebo/no treatment and separate AEs [MI, cerebrovascular accident (ischaemic and haemorrhagic strokes) and cardiovascular death] or MACEs in each intervention group. Since MACEs are serious AEs, all of these events should be reported. If the RCTs did not report the number of separate AEs or MACEs, it was assumed that no MACEs occurred.

For extension RCTs in which treatment assignments were switched (for instance, patients who were initially treated with placebo switched to a biologic therapy), only MACEs before that point were documented. For multiple reports on the same RCT, all data were collated and aligned to a single RCT. If MACEs were reported at multiple follow-up points, data from the longest randomised follow-up were selected provided there was a continuation of the control arm. The overall number of MACEs during the randomised controlled phase in the treatment and control groups of the individual RCTs was extracted for patients who received at least one dose of study agent or placebo; or did not receive any treatment.

The Cochrane quality assessment tool for RCTs[365] was used for assessing risk of bias. Eight domains including sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data (defined as missing outcome data owing to patients dropping out during the study period or excluded from the analysis), selective outcome reporting, adjudication of MACEs and baseline imbalance were considered.

5.3.5 Data analysis

Extracted data were combined for the meta-analysis using Review Manager (RevMan) 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Peto ORs were calculated as an effect measure to quantify the risk of MACEs in patients receiving biologic therapies compared with placebo/no treatment or the same biologic with different dosing. The Peto OR has been reported to perform better than other meta-analytical methods for rare event rates (lower than 1%).[366]

There were six main comparisons which included: 1) any biologic therapies (TNFi, anti-IL-17A agents and anti-IL-12/23 agent) against placebo/no treatment; 2) TNFi against placebo; 3) anti-IL-17A agents (secukinumab and ixekizumab) against placebo; 4) anti-IL-12/23 agent (ustekinumab) against placebo; 5) ustekinumab 45 mg against 90 mg; and 6) secukinumab 150 mg against 300 mg. In the first four comparisons, all licensed doses of biologic therapies were considered.

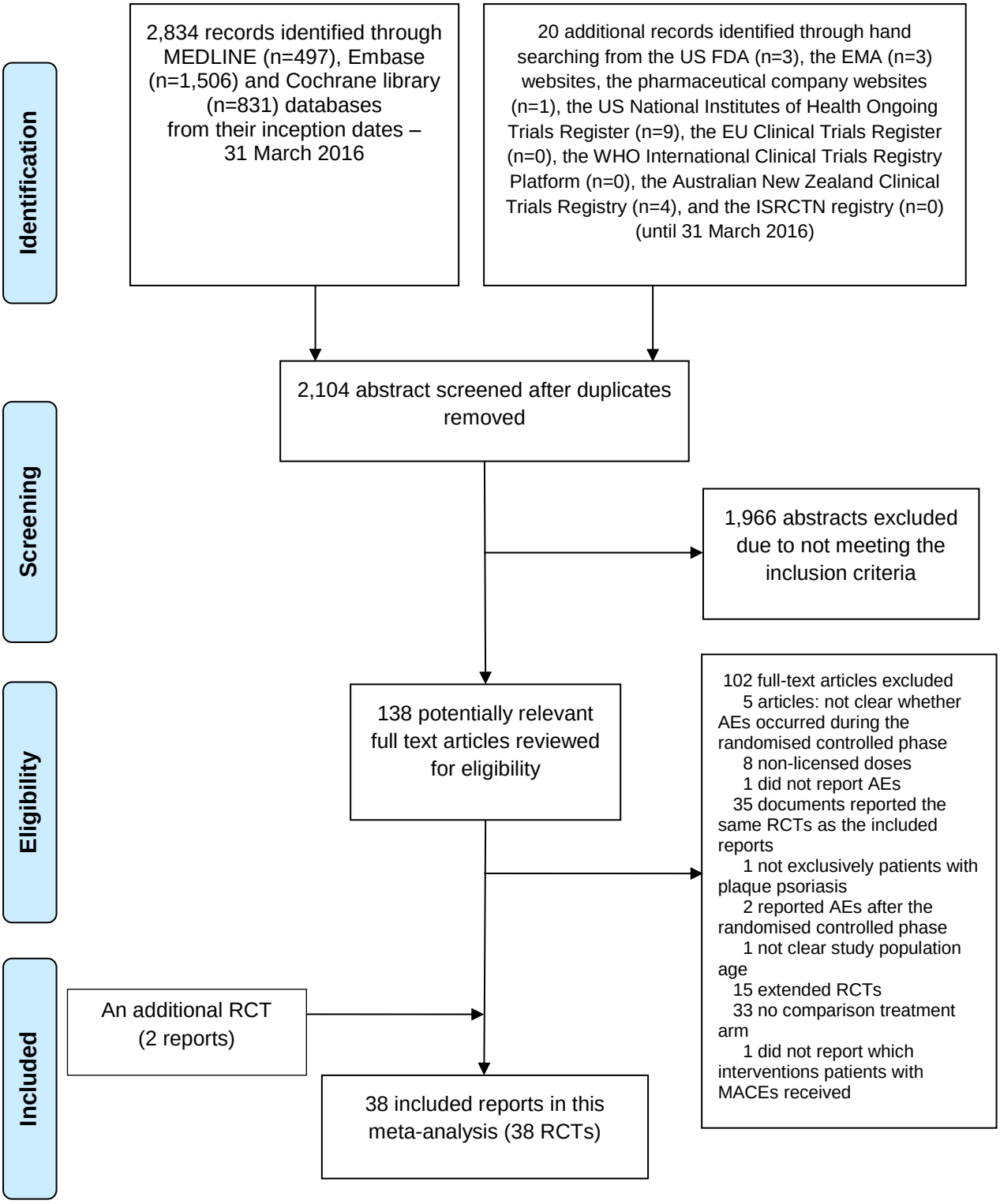
A sensitivity analysis was also undertaken using the Mantel-Haenszel risk difference to explore whether analysis methods had an influence on the results of the comparisons. This method (unlike the Peto OR) does not exclude RCTs without MACEs in both comparison groups.[366] Heterogeneity between studies was assessed using the χ^2 test (p-value < 0.05 was considered statistically significant) and I^2 statistics (I^2 > 50%: significant heterogeneity; I^2 < 40%: insignificant heterogeneity). Funnel plot analysis was used for detection of potential publication bias.[367]

5.4 Results

5.4.1 Study selection

In all, 38 RCTs (identified in 38 reports[260,261,368–403]) met the eligibility criteria and were included, as shown in Figure 5.1. These trials involved a total of 18,024 patients with plaque psoriasis. The 38 RCTs were conducted in 1 - 231 (median 47) study sites. Thirty-five RCTs (92.1%) were double-blind studies. The length of the randomised controlled phase ranged from 10 to 30 (median 12) weeks. The included studies involved 20 - 1,303 patients with plaque psoriasis with the percentage of male patients ranging from 53 - 90%, percentage with psoriatic arthritis from 3 - 37%, mean age range 39.2 - 55.7 years, mean duration of psoriasis range 11.9 - 21.5 years, mean PASI range 11.5 - 30.3 (Table 5.1).

Figure 5.1 PRISMA Flowchart of the included randomised controlled trials



Abbreviations: AE, adverse event; EMA, European Medicine Agency; FDA, Food and Drug Administration; ISRCTN, International Standard Randomised Controlled Trial Number; RCT, randomised controlled trial; WHO, World Health Organisation

Table 5.1 Characteristics of the included randomised controlled trials

Authors, year	Number of study sites	Masking	Randomised controlled-phase (weeks)	Interventions during randomised controlled-phase	Number of participants receiving treatment	Mean age ± SD (median) years	Male, n (%)	History of psoriatic arthritis, n (%)	Mean weight ± SD (median) kg	Mean duration of psoriasis ± SD (median) years	Mean PASI score ± SD (median)	Mean BSA ± SD (median) (%)	Rate of missing patient data
Adalimumab vs placebo													
Menter et.al., 2008 (REVEAL)[378]	81	Double-blind	16	Adalimumab 80 mg SC. at week 0 followed by 40 mg SC. EOW starting at week 1	814	44.1 ± 13.2	546 (67.1)	224 (27.5)	92.3 ± 23.0	18.1 ± 11.91	19.0 ± 7.08	25.8 ± 15.51	3.8%
				Placebo at week 0 then EOW starting at week 1	398	45.4 ± 13.4	257 (64.6)	113 (28.4)	94.1 ± 23.0	18.4 ± 11.94	18.8 ± 7.09	25.6 ± 14.76	10.8%
Maari et.al., 2014[389]	1	Double-blind	12	Adalimumab 80 mg followed by 40 mg at week 1 and then 40 mg EOW for 7 weeks	10	55.7 ± 11.8	9 (90)	NR	132.0 ± 22.2	NR	11.5 ± 6.3	12.5 ± 11.0	0%
				Placebo for 7 weeks	10	49.0 ± 10.9	9 (90)	NR	135.9 ± 31.5	NR	10.4 ± 4.5	10.0 ± 5.0	0%
Gordon et.al., 2015 (X-PLORE)[398]	43	Double-blind	16	Adalimumab 80 mg SC. at week 0 and then 40 mg EOW starting at week 1	43	(50.0)	30 (69.8)	11 (25.6)	91.6 ± 19.88	19.3 ±12.79	20.2 ± 7.58 (17.9)	26.8 ± 16.80	9.3%
				Placebo SC.	42	(46.5)	28 (66.7)	12 (28.6)	93.6 ± 22.62	18.0 ± 13.30	21.8 ± 9.98 (17.3)	27.5 ± 19.26	7.1%
AbbVie 2015, NCT01646073, clinicaltrials.gov[399]	16	Double-blind	12	Adalimumab 80 mg SC. at week 0 followed by 40 mg SC. EOW starting at week 1[400]	338	43.1 ± 11.91	254 (75.1)	NR	NR	14.8 ± 10.11	28.2 ± 12.00	42.6 ± 21.75	1.5%
				Placebo SC. at week 0 and EOW starting at week 1[400]	87	43.8 ± 12.45	58 (66.7)	NR	NR	15.8 ± 10.31	25.60 ± 10.98	39.3 ± 22.50	2.4%
Adalimumab vs methotrexate													
Goldminz et.al., 2015[394]	1	Open-label	16	Adalimumab 80 mg SC. at week 0 followed by 40 mg SC. EOW	15	50.5	11 (73.3)	2 (13.3)	NR	17.3 (1 - 45)	16.8	NR	6.7%

Authors, year	Number of study sites	Masking	Randomised controlled-phase (weeks)	Interventions during randomised controlled-phase	Number of participants receiving treatment	Mean age ± SD (median) years	Male, n (%)	History of psoriatic arthritis, n (%)	Mean weight ± SD (median) kg	Mean duration of psoriasis ± SD (median) years	Mean PASI score ± SD (median)	Mean BSA ± SD (median) (%)	Rate of missing patient data
				Methotrexate 7.5 - 25 mg/week orally	15	50.3	13 (86.7)	3 (20.0)	NR	21.5 (0 - 47)	15.9	NR	0%
Adalimumab vs methotrexate vs placebo													
Saurat et.al., 2008 (CHAMPION)[260]	28	Double-blind	16	Adalimumab 80 mg SC. at week 0 followed by 40 mg SC. EOW starting at week 1	107	42.9 ± 12.6	70 (64.8)	23 (21.3)	81.7 ± 20.0	17.9 ± 10.1	20.2 ± 7.5	33.6 ± 19.9	3.7%
				Methotrexate 7.5 - 25 mg/week orally	110	41.6 ± 12.0	73 (66.4)	19 (17.3)	83.1 ± 17.5	18.9 ± 10.2	19.4± 7.4	32.4 ± 20.6	5.5%
				Placebo	53	40.7 ± 11.4	35 (66.0)	11 (20.8)	82.6 ± 19.9	18.8 ± 8.7	19.2 ± 6.9	28.4 ± 16.1	9.4%
Etanercept vs placebo													
Gottlieb et.at., 2003[401]	Multicentres	Double-blind	24	Etanercept 25 mg SC. BIW	57	48.2	33 (58)	16 (28.1)	91.8	23	17.8	30	15.8%
				Placebo SC. BIW	55	46.5	37 (67)	19 (34.5)	90.7	20	19.5	34	78.2%
Tyring et.al., 2006[402]	39	Double-blind	12	Etanercept 50 mg SC. BIW	312	45.8 ± 12.8	203 (65.3)	109 (35.0)	NR	20.1 ± 12.3	18.3 ± 7.6	27.2 ± 18.2	1.9%
				Placebo SC. BIW	306	45.6 ± 12.1	216 (70.4)	100 (32.6)	NR	19.7 ± 11.4	18.1 ± 7.4	27.2 ± 17.2	5.5%
van de Kerkhof et.al., 2008[403]	NR	Double-blind	12	Etanercept 50 mg SC. QW	96	45.9 ± 12.8	59 (61.5)	15 (15.6)	83.4 ± 16.0	19.3 ± 11.3	21.4 ± 9.3	26.5 ± 15.0	6.3%
				Placebo SC. QW	46	43.6 ± 12.6	25 (54.4)	5 (10.9)	79.1 ± 20.2	17.3 ± 8.2	21.0 ± 8.7	30.3 ± 17.8	21.7%
Gottlieb et.al., 2011[368]	33	Double-blind	12	Etanercept 50 mg SC. BIW week 0 - 11	141	43.1 ± 12.5	98 (69.5)	32 (22.7)	94.5 ± 20.4	17.0 ± 12.7	19.4 ± 8.0	24.1 ± 15.0	5.0%
				Placebo SC. matching active treatment	68	44.0 ± 13.6	47 (69.1)	14 (20.6)	96.5 ± 27.2	19.1 ± 13.2	18.5 ± 6.9	23.8 ± 15.5	7.4%
Strober et.al., 2011[369]	41	Double-blind	12	Etanercept 50 mg SC. BIW week 0 - 11	139	45.2 ± 14.8	85 (61.2)	46 (33.1)	96.9 ± 24.9	15.2 ± 12.1	18.5 ± 6.0	24.7 ± 13.9	8.6%

Authors, year	Number of study sites	Masking	Randomised controlled-phase (weeks)	Interventions during randomised controlled-phase	Number of participants receiving treatment	Mean age ± SD (median) years	Male, n (%)	History of psoriatic arthritis, n (%)	Mean weight ± SD (median) kg	Mean duration of psoriasis ± SD (median) years	Mean PASI score ± SD (median)	Mean BSA ± SD (median) (%)	Rate of missing patient data
				Placebo SC. matching active treatment	72	45.0 ± 13.9	46 (63.9)	15 (20.8)	92.9 ± 25.2	15.5 ± 11.7	18.3 ± 6.4	22.1 ± 13.4	8.3%
Bagel et.al., 2012[370]	NR	Double-blind	12	Etanercept 50 mg SC. BIW	59	(39)	33 (53.2)	NR	NR	(17.5)	(15.5)	(15.5)	NR
				Placebo SC. BIW	62	(42)	36 (58.1)	NR	NR	(11.9)	(15.2)	(15.0)	NR
Bachelez et.al., 2015[371]	122	Doule blind	12	Etanercept 50 mg SC. BIW	335	(42.0)	233 (69.6)	71 (21.2)	NR	(18.0)	(19.4)	(25.0)	6.8%
				Placebo	107	(46.0)	71 (66.4)	26 (21.2)	NR	(17.0)	(19.5)	(26.0)	12.0%
Etanercept (different strengths) vs placebo													
Leonardi et.al., 2003[373]	47	Double-blind	12	Etanercept 25 mg SC. QW	160	44.4	118 (74)	NR	NR	19.3	18.2	27.7	NR
				Etanercept 25 mg SC. BIW	162	45.4	109 (67)	NR	NR	18.5	18.5	28.5	NR
				Etanercept 50 mg SC. BIW	164	44.8	107 (65)	NR	NR	18.6	18.4	29.9	NR
				Placebo	166	45.6	105 (63)	NR	NR	18.4	18.3	28.8	NR
Papp et.al., 2005[374]	50	Double-blind	12	Etanercept 25 mg SC. BIW	196	(46.0)	128 (65.3)	54 (27.6)	NR	(21.5)	(16.9)	(23.0)	2.6%
				Etanercept 50 mg SC. BIW	194	(44.5)	130 (67.0)	50 (25.8)	NR	(18.1)	(16.1)	(25.0)	2.1%
				Placebo SC. BIW	193	(44.0)	124 (64.2)	50 (25.9)	NR	(17.5)	(16.0)	(20.0)	7.8%
Etanercept vs ixekizumab vs placebo													
Griffiths et.al., 2015 (UNCOVER-2)[372]	126	Double-blind	12	Etanercept 50 mg SC. BIW	357	45 ± 13	236 (66)	NR	NR	19 ± 12	19 ± 7	25 ± 16	7.0%
				Ixekizumab 160 mg SC. week 0 then 80 mg SC. every 2 weeks	350	45 ± 13	221 (63)	NR	NR	18 ± 12	19 ± 7	25 ± 16	2.6%
				Placebo	167	45 ± 12	120 (71)	NR	NR	19 ± 13	21 ± 8	27 ± 18	6.0%
Griffiths et.al., 2015 (UNCOVER-3)[372]	126	Double-blind	12	Etanercept 50 mg SC. BIW	382	46 ± 14	269 (70)	NR	NR	18 ± 12	21 ± 8	28 ± 17	3.4%
				Ixekizumab 160 mg SC. week 0 then 80 mg SC. every 2 weeks	384	46 ± 13	254 (66)	NR	NR	18 ± 12	21 ± 8	28 ± 17	5.7%

Authors, year	Number of study sites	Masking	Randomised controlled-phase (weeks)	Interventions during randomised controlled-phase	Number of participants receiving treatment	Mean age ± SD (median) years	Male, n (%)	History of psoriatic arthritis, n (%)	Mean weight ± SD (median) kg	Mean duration of psoriasis ± SD (median) years	Mean PASI score ± SD (median)	Mean BSA ± SD (median) (%)	Rate of missing patient data
				Placebo	193	46 ± 12	137 (71)	NR	NR	18 ± 13	21 ± 8	29 ± 17	5.2%
Infliximab vs placebo													
Chaudhari et.al., 2001[375]	1	Double-blind	10	Infliximab 5 mg/ml IV. at week 0, 2 and 6	11	51 ± 14	7 (63.6)	NR	87 ± 20	NR	22.1 ± 11.5	NR	9.1%
				Placebo IV. at week 0, 2 and 6	11	45 ± 12	8 (72.7)	NR	85 ± 19	NR	20.3 ± 5.5	NR	9.1%
Gottlieb et.al., 2004 (SPIRIT)[376]	24	Double-blind	30	Infliximab 5 mg/kg IV. infusion at week 0, 2 and 6 At week 26, if patients had a static PGA of moderate to severe disease, they received a single additional IV. infusion of infliximab 5 mg/kg.	99	(44)	73 (73.7)	29 (29.3)	NR	(16)	(20)	(25)	18.2%
				Placebo IV. infusion at week 0, 2 and 6 At week 26, if patients had a static PGA of moderate to severe disease, they received a single additional IV. infusion of placebo	51	(45)	31 (60.0)	17 (33.3)	NR	(16)	(18)	(26)	72.5%
Reich et.al., 2005 (EXPRESS)[377]	32	Double-blind	24	Infliximab 5 mg/kg IV at week 0, 2 and 6 and every 8 weeks	298	42.6 ± 11.7	207 (68.77)	92 (31)	NR	19.1 ± 11.0	22.9 ± 9.3	34.1 ± 19	10.6%
				Placebo at week 0, 2, 6, 14 and 22	76	43.8 ± 12.6	61 (79.22)	22 (29)	NR	17.3 ± 11.1	22.8 ± 8.7	33.5 ± 18	11.7%
Menter et.al., 2007 (EXPRESS II)[379]	63	Double-blind	14	Infliximab 5 mg/kg infusion at week 0, 2 and 6	314	44.5 ± 13.0 (44.0)	204 (65.0)	89 (28.3)	92.2 ± 23.2 (88.8)	19.1 ± 11.7 (17.9)	20.4 ± 7.5 (18.6)	28.7 ± 16.4 (24.0)	5.4%
				Placebo infusion at week 0, 2 and 6	207	44.4 ± 12.5 (44.5)	144 (69.2)	54 (26.0)	91.1 ± 22.6 (88.9)	17.8 ± 10.8 (16.1)	19.8 ± 7.7 (17.4)	28.4 ± 17.6 (22.0)	11.5%
Yang et.al., 2012[380]	9	Double-blind	10	Infliximab 5 mg/kg IV drip infusion week 0, 2 and 6	84	39.4 ± 12.3	60 (71.4)	NR	68.2 ± 9.2	16.0 ± 10.8	23.9 ±10.7	NR	1.2%
				Placebo IV drip infusion week 0, 2	45	40.1 ± 11.1	35 (77.8)	NR	67.4 ± 9.9	16.0 ± 8.9	25.3 ± 12.7	NR	2.2%

Authors, year	Number of study sites	Masking	Randomised controlled-phase (weeks)	Interventions during randomised controlled-phase	Number of participants receiving treatment	Mean age ± SD (median) years	Male, n (%)	History of psoriatic arthritis, n (%)	Mean weight ± SD (median) kg	Mean duration of psoriasis ± SD (median) years	Mean PASI score ± SD (median)	Mean BSA ± SD (median) (%)	Rate of missing patient data
				and 6									
Infliximab vs methotrexate													
Barker et.al., 2011 (RESTORE1)[261]	106	Open-label	16	Inflximab 5 mg/kg at weeks 0, 2, 6, 14 and 22	649	44.1	438 (67)	NR	84.5 ± 18.6	18.8 ± 11.6	21.4 ± 8.0	31.9 ± 16.5	NR
				Methotrexate 15 mg weekly with a dose increase to 20 mg weekly at week 6 if PASI response < 25%	211	41.9	148 (69)	NR	83.8 ± 18.2	17.0 ± 10.3	21.1 ± 7.6	31.0 ± 15.0	NR
Ixekizumab vs placebo													
Gordon et.al., 2016 (UNCOVER-1)[397]	110	Double-blind	12	Ixekizumab 160 mg SC. week 0 then 80 mg SC. every 2 weeks	433	45 ± 12	291 (67.2)	NR	92 ± 23[396]	20 ± 12	20 ± 8	28 ± 18	4.2%
				Placebo SC week 0 then every 2 weeks	431	46 ± 13	303 (70.3)	NR	92 ± 25[396]	20 ± 12	20 ± 9	27 ± 18	5.6%
Secukinumab 150 mg vs secukinumab 300 mg													
Mrowietz et.al., 2015 (SCULPTURE)[381]	133	Double-blind	12	Secukinumab 150 mg SC. at week 0, 1, 2, 3, 4 and 8	482	45.3 ± 12.83	305 (63.3)	104 (21.6)	85.2 ± 22.75	17.2 ± 12.71	24.0 ± 10.44	35.7 ± 21.09	3.7%
				Secukinumab 300 mg SC. at week 0, 1, 2, 3, 4 and 8	483	46.7 ± 12.83	333 (68.8)	94 (19.4)	85.1 ± 23.20	17.4 ± 12.88	23.3 ± 9.56	33.7 ± 19.56	4.1%
Secukinumab 150 mg vs secukinumab 300 mg vs placebo													
Langley et.al., 2014 (ERASURE)[382]	88	Double-blind	12	Secukinumab 150 mg SC. at week 0, 1, 2, 3, 4 and then every 4 weeks	245	44.9 ± 13.3	168 (68.6)	46 (18.8)	87.1 ± 22.3	17.5 ± 12.0	22.3 ± 9.8	33.3 ± 19.2	6.1%
				Secukinumab 300 mg SC. at week 0, 1, 2, 3, 4 and then every 4 weeks	245	44.9 ± 13.5	169 (69.0)	57 (23.3)	88.8 ± 24.0	17.4 ± 11.1	22.5 ± 9.2	32.8 ± 19.3	2.9%
				Placebo at week 0, 1, 2, 3, 4 and then every 4 weeks	247	45.4 ± 12.6	172 (69.4)	68 (27.4)	89.7 ± 25.0	17.3 ± 12.4	21.4 ± 9.1	29.7 ± 15.9	6.5%

Authors, year	Number of study sites	Masking	Randomised controlled-phase (weeks)	Interventions during randomised controlled-phase	Number of participants receiving treatment	Mean age ± SD (median) years	Male, n (%)	History of psoriatic arthritis, n (%)	Mean weight ± SD (median) kg	Mean duration of psoriasis ± SD (median) years	Mean PASI score ± SD (median)	Mean BSA ± SD (median) (%)	Rate of missing patient data
Blauvelt et.al., 2015 (FEATURE)[383]	32	Double-blind	12	Secukinumab 150 mg SC. week 0, 1, 2, 3, 4 and 8	59	46.0 ± 15.09	40 (67.8)	NR	93.7 ± 25.64	20.4 ± 12.97	20.5 ± 8.29	30.6 ± 16.65	1.7%
				Secukinumab 300 mg SC. week 0, 1, 2, 3, 4 and 8	59	45.1 ± 12.57	38 (64.4)	NR	92.6 ± 25.94	18.0 ± 11.86	20.7 ± 7.95	33.3 ± 17.98	5.1%
				Placebo SC. week 0, 1, 2, 3, 4 and 8	59	46.5 ± 14.14	39 (66.1)	NR	88.4 ± 21.55	20.2 ± 14.22	21.1 ± 8.49	32.2 ± 17.39	5.1%
Paul et.al., 2015 (JUNCTURE)[384]	38	Double-blind	12	Secukinumab 150 mg SC.week 0, 1, 2, 3, 4 and 8	61	43.9 ± 14.41	41 (67.2)	16 (26.2)	93.7 ± 31.71	20.6 ± 14.54	22.0 ± 8.85	30.1 ± 16.66	4.9%
				Secukinumab 300 mg SC.week 0, 1, 2, 3, 4 and 8	60	46.6 ± 14.23	46 (76.7)	14 (23.3)	91.0 ± 23.13	21.0 ± 13.51	18.9 ± 6.37	26.4 ± 12.77	0%
				Placebo SC.week 0, 1, 2, 3, 4 and 8	61	43.7 ± 12.74	38 (62.3)	12 (19.7)	90.2 ± 21.16	19.86 ± 12.20	19.4 ± 6.70	25.7 ± 14.70	3.3%
Ustekinumab vs placebo													
Tsai et.al., 2011 (PEARL)[385]	13	Double-blind	12	Ustekinumab 45 mg SC. at week 0 and 4	61	40.9 ± 12.7	50 (82.0)	10 (16.4)	73.1 ± 12.7	11.9 ± 7.5	25.2 ± 11.9	41.8 ± 24.4	6.6%
				Placebo SC. at week 0 and 4	60	40.4 ± 10.1	53 (88.3)	7 (11.7)	74.6 ± 13.0	13.9 ± 7.3	22.9 ± 8.6	35.8 ± 21.4	8.3%
Zhu et.al., 2013 (LOTUS)[386]	14	Double-blind	12	Ustekinumab 45 mg SC. at week 0 and 4	160	40.1 ± 12.4	125 (78.1)	14 (8.8)	69.9 ± 11.9	14.6 ± 8.9	23.2 ± 9.5	35.1 ± 18.5	1.9%
				Placebo SC. at week 0 and 4	161	39.2 ± 12.2	123 (75.9)	14 (8.6)	70.0 ± 12.6	14.2 ± 8.6	22.7 ± 9.5	35.1 ± 19.6	1.9%
Lebwohl et.al., 2015 (AMAGINE 2) [387]	142	Double-blind	12	Ustekinumab SC. (45 mg for patients with a body weight ≤ 100 kg and 90 mg for patients with a body weight > 100 kg) on day 1 and week 4	300	45 ± 13	205 (68.3)	50 (16.7)	91 ± 24	19 ± 13	20. ± 8.4	27 ± 19	3.0%
				Placebo	309	44 ± 13	219 (70.9)	51 (16.5)	92 ± 23	18 ± 12	20.4 ± 8.2	28 ± 17	2.9%
Lebwohl et.al., 2015 (AMAGINE 3)[387]	142	Double-blind	12	Ustekinumab SC. (45 mg for patients with a body weight ≤ 100 kg and 90 mg for	313	45 ± 13	212 (67.7)	64 (20.4)	90 ± 22	18 ± 12	20.1 ± 8.4	28 ± 18	3.2%

Authors, year	Number of study sites	Masking	Randomised controlled-phase (weeks)	Interventions during randomised controlled-phase	Number of participants receiving treatment	Mean age ± SD (median) years	Male, n (%)	History of psoriatic arthritis, n (%)	Mean weight ± SD (median) kg	Mean duration of psoriasis ± SD (median) years	Mean PASI score ± SD (median)	Mean BSA ± SD (median) (%)	Rate of missing patient data
				patients with a body weight > 100 kg) on day 1 and week 4									
				Placebo	315	44 ± 13	208 (66.0)	59 (18.7)	89 ± 22	18 ± 12	20.1 ± 8.7	28 ± 17	4.4%
Ustekinumab 45 mg vs ustekinumab 90 mg vs placebo													
Leonardi et.al., 2008 (PHOENIX 1)[391]	48	Double-blind	12	Ustekinumab 45 mg SC. at week 0 and 4	255	44.8 ± 12.5	175 (68.6)	74 (29.0)	93.7 ± 23.8	19.7 ± 11.7	20.5 ± 8.6	27.2 ± 17.5	0.4%
				Ustekinumab 90 mg SC. at week 0 and 4	255	46.2 ± 11.3	173 (67.6)	95 (37.1)	93.8 ± 23.9	19.6 ± 11.1	19.7 ± 7.6	25.2 ± 15.0	4.3%
				Placebo at week 0 and 4	255	44.8 ± 11.3	183 (71.8)	90 (35.3)	94.2 ± 3.5	20.4 ± 11.7	20.4 ± 8.6	27.7 ± 17.4	4.7%
Papp et.al., 2008 (PHOENIX 2)[388]	70	Double-blind	12	Ustekinumab 45 mg SC. at week 0 and 4	409	45.1 ± 12.1	283 (69.2)	107 (26.2)	90.3 ± 21.0	19.3 ± 11.7	19.4 ± 6.8	25.9 ± 15.5	1.5%
				Ustekinumab 90 mg SC. at week 0 and 4	411	46.6 ± 12.1	274 (66.7)	94 (22.9)	91.5 ± 21.3	20.3 ± 12.3	20.1 ± 7.5	27.1 ± 17.4	2.2%
				Placebo	410	47.0 ± 12.5	283 (69.0)	105 (25.6)	91.1 ± 21.6	20.8 ± 12.2	19.4 ± 7.5	26.1 ± 17.4	4.4%
Igarashi et.al, 2012[390]	35	Double-blind	12	Ustekinumab 45 mg SC. at week 0 and 4	64	46.6 ± 12.5 (45)[390,395]	53 (82.8)	6 (9.4)	73.2 ± 15.4	15.8 ± 8.2	30.1 ± 12.9	47.0 ± 23.7	0%
				Ustekinumab 90 mg SC. at week 0 and 4	62	46.8 ± 12.8 (44)[390,395]	47 (75.8)	7 (11.3)	71.1 ± 14.0	17.3 ± 10.7	28.7 ± 11.2	46.6 ± 19.7	6.5%
				Placebo SC. at week 0 and 4	32	48.5 ± 12.7 (49)[390,395]	26 (83.9)	1 (3.1)	71.2 ± 10.9	16.0 ± 11.2	30.3 ± 11.8	49.8 ± 22.5	12.5%
Etanercept vs ustekinumab 45 mg vs ustekinumab 90 mg													
Griffiths et.al., 2010 (ACCEPT)[392]	67	Double-blind	12	Etanercept 50 mg SC. BIW	347	45.7 ± 13.4	246 (70.9)	95 (27.4)	90.8 ± 20.9	18.8 ± 12.1	18.6 ± 6.2	23.8 ± 13.9	3.2%
				Ustekinumab 45 mg SC. at week 0 and 4	209	45.1 ± 12.6	133 (63.6)	62 (29.7)	90.4 ± 21.1	18.9 ± 11.8	20.5 ± 9.2	26.7 ± 17.8	3.8%
				Ustekinumab SC. 90 mg SC. at week 0 and 4	347	44.8 ± 12.3	234 (67.4)	95 (27.4)	91.0 ± 22.8	18.7 ± 11.8	19.9 ± 8.4	26.1 ± 17.6	1.4%

Authors, year	Number of study sites	Masking	Randomised controlled-phase (weeks)	Interventions during randomised controlled-phase	Number of participants receiving treatment	Mean age ± SD (median) years	Male, n (%)	History of psoriatic arthritis, n (%)	Mean weight ± SD (median) kg	Mean duration of psoriasis ± SD (median) years	Mean PASI score ± SD (median)	Mean BSA ± SD (median) (%)	Rate of missing patient data
Etanercept vs ustekinumab vs no treatment													
Merck Sharp & Dohme 2015, NCT01276847, clinicaltrials.gov[393]	NR	Open label	16	Etanercept 50 mg SC. BIW for 12 weeks then SC. QW for 4 weeks	10	39.5 ± 12.5	6 (60.0)	NR	NR	NR	NR	NR	10%
				Ustekinumab 45 mg SC. for participants weighing ≤ 100 kg, and ustekinumab 90 mg SC. for participants weighing > 100 kg on day 1, and weeks 4 and 16	20	45.7 ± 12.1	13 (65.0)	NR	NR	NR	NR	NR	0%
				No Treatment	10	53.4 ± 13.0	9 (90.0)	NR	NR	NR	NR	NR	0%
Etanercept vs secukinumab 150 mg vs secukinumab 300 mg vs placebo													
Langley et.al., 2014 (FIXTURE)[382]	231	Double-blind	12	Etanercept 50 mg SC. BIW	323	43.8 ± 13.0	232 (71.2)	44 (13.5)	84.6 ± 20.5	16.4 ± 12.0	23.2 ± 9.8	33.6 ± 18.0	6.4%
				Secukinumab 150 mg SC. QW week 0, 1, 2, 3, 4 and then every 4 weeks	327	45.4 ± 12.9	236 (72.2)	49 (15.0)	83.6 ± 20.8	17.3 ± 12.2	23.7 ± 10.5	34.5 ± 19.4	3.7%
				Secukinumab 300 mg SC. QW week 0, 1, 2, 3, 4 and then every 4 weeks	326	44.5 ± 13.2	224 (68.5)	50 (15.3)	83.0 ± 21.6	15.8 ± 12.3	23.9 ± 9.9	34.3 ± 19.2	4.6%
				Placebo at weeks corresponding to etanercept and secukinumab regimens	327	44.1 ± 12.6	237 (72.7)	49 (15.0)	82.0 ± 20.4	16.6 ± 11.6	24.1 ± 10.5	35.2 ± 19.1	7.7%

Abbreviations: BIW, twice weekly; BSA, body surface area; EOW, every other week; IV., intravenous; NR, not reported; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; QW, once weekly; SC., subcutaneous; SD, standard deviation

Eighteen RCTs compared TNFi (four adalimumab[378,389,398–400], nine etanercept[368–371,373,374,401–403], five infliximab[375–377,379,380]) to placebo, with three studies reporting MACEs; while four RCTs compared ustekinumab (anti-IL-12/23 agent) with placebo[385–387] with no MACEs reported. One RCT compared ixekizumab (anti-IL-17A agent) with placebo without MACEs reported.[396,397] Six RCTs compared different dose regimens of ustekinumab (three RCTs)[388,390,391] or secukinumab (anti-IL-17A agent, three RCTs)[382–384] with placebo, with four MACEs reported from three RCTs. One RCT compared ustekinumab 45 mg and 90 mg with etanercept but no MACEs were observed.[392] Secukinumab 150 mg was compared against 300 mg in one RCT and one patient experienced a MACE in the 300 mg dose group.[381] Etanercept (TNFi) was compared with ustekinumab[393], secukinumab[382], ixekizumab[372] and placebo/no treatment in four RCTs but only two of them reported two MACEs. One RCT compared adalimumab (TNFi) with placebo and methotrexate[260], one RCT compared adalimumab with methotrexate[394] and one RCT compared infliximab (TNFi) with methotrexate[261]; no patients in these studies experienced a MACE (Table 5.2).

The overall MACE rates were 0.06% (n=8) for any biologic therapies (total patients 12,596), 0.05% (n=3) for TNFi (total patients 6,216), 0.09% (n=3) for anti-IL-17A agents (secukinumab and ixekizumab) (total patients 3,514), 0.07% (n=2) for ustekinumab (total patients 2,866), 0.04% (n=2) for placebo (total patients 5,092) and 0% (n=0) for methotrexate (total patients 336). Seventeen RCTs reported the outcomes using an aggregate MACE definition (this included a study by Papp et.al., 2008 which used the term “cardiovascular events” instead of MACEs but its definition was the same as the definition of MACEs in this study.) while 21 RCTs reported AEs separately.

Table 5.2 Numbers of major adverse cardiovascular events in the included randomised controlled trials

Authors, year	Interventions	Number of participants receiving treatment	MACEs	Randomised controlled-phase (weeks)
Adalimumab vs placebo				
Menter et.al., 2008 (REVEAL)[378]	Adalimumab 80 mg SC. at week 0 followed by 40 mg SC. EOW starting at week 1	814	0	16
	Placebo at week 0 then EOW starting at week 1	398	0	
Maari et.al., 2014[389]	Adalimumab 80 mg followed by 40 mg at week 1 and then 40 mg EOW for 7 weeks	10	0	12
	Placebo for 7 weeks	10	0	
Gordon et.al., 2015 (X-PLORE) [398]	Adalimumab 80 mg SC. at week 0 and then 40 mg EOW starting at week 1	43	0	16
	Placebo SC.	42	0	
AbbVie, 2015, NCT01646073, ClinicalTrials.gov, 2015[399]	Adalimumab 80 mg SC. at week 0 followed by 40 mg SC. EOW starting at week 1[400]	338	1	12
	Placebo SC. at week 0 and EOW starting at week 1[400]	87	0	
Adalimumab vs methotrexate				
Goldminz et.al., 2015[394]	Adalimumab 80 mg SC. at week 0 followed by 40 mg SC. EOW	15	0	16
	Methotrexate 7.5 - 25 mg/week orally	15	0	
Adalimumab vs methotrexate vs placebo				
Saurat et.al., 2008 (CHAMPION)[260]	Adalimumab 80 mg SC. at week 0 followed by 40 mg SC. EOW starting at week 1	107	0	16
	Methotrexate 7.5 - 25 mg/week orally	110	0	
	Placebo	53	0	
Etanercept vs placebo				
Gottlieb et.at., 2003[401]	Etanercept 25 mg SC. BIW	57	0	24
	Placebo SC. BIW	55	1	
Tyring et.al., 2006[402]	Etanercept 50 mg SC. BIW	312	0	12
	Placebo SC. BIW	306	0	
van de Kerkhof et.al., 2008[403]	Etanercept 50 mg SC. QW	96	0	12
	Placebo SC. QW	46	0	
Gottlieb et.al., 2011[368]	Etanercept 50 mg SC. BIW week 0 - 11	141	0	12
	Placebo SC. matching active treatment	68	0	
Strober et.al., 2011[369]	Etanercept 50 mg SC. BIW week 0 - 11	139	0	12
	Placebo SC. matching active treatment	72	0	
Bagel et.al., 2012[370]	Etanercept 50 mg SC. BIW	59	0	12
	Placebo SC. BIW	62	0	

Authors, year	Interventions	Number of participants receiving treatment	MACEs	Randomised controlled-phase (weeks)
Bachelez et.al., 2015[371]	Etanercept 50 mg SC. BIW	335	1	12
	Placebo	107	0	
Etanercept (different strengths) vs placebo				
Leonardi et.al., 2003[373]	Etanercept 25 mg SC. QW	160	0	12
	Etanercept 25 mg SC. BIW	162	0	
	Etanercept 50 mg SC. BIW	164	0	
	Placebo	166	0	
Papp et.al., 2005[374]	Etanercept 25 mg SC. BIW	196	0	12
	Etanercept 50 mg SC. BIW	194	0	
	Placebo SC. BIW	193	0	
Etanercept vs ixekizumab vs placebo				
Griffiths et.al., 2015 (UNCOVER-2)[372]	Etanercept 50 mg SC. BIW	357	1	12
	Ixekizumab 160 mg SC. week 0 then 80 mg SC. every 2 weeks	350	0	
	Placebo	167	0	
Griffiths et.al., 2015 (UNCOVER-3)[372]	Etanercept 50 mg SC. BIW	382	0	12
	Ixekizumab 160 mg SC. week 0 then 80 mg SC. every 2 weeks	384	0	
	Placebo	193	1	
Infliximab vs placebo				
Chaudhari et.al., 2001[375]	Infliximab 5 mg/ml IV. at week 0, 2 and 6	11	0	10
	Placebo IV. at week 0, 2 and 6	11	0	
Gottlieb et.al., 2004 (SPIRIT) [376]	Infliximab 5 mg/kg IV. infusion at week 0, 2 and 6 At week 26, if patients had a static PGA of moderate to severe disease, they received a single additional IV. infusion of infliximab 5 mg/kg	99	0	30
	Placebo IV. infusion at week 0, 2 and 6 At week 26, if patients had a static PGA of moderate to severe disease, they received a single additional IV. infusion of placebo	51	0	
Reich et.al., 2005 (EXPRESS)[377]	Infliximab 5 mg/kg IV. at week 0, 2 and 6 and every 8 weeks	298	0	24
	Placebo at week 0, 2, 6, 14 and 22	76	0	
Menter et.al., 2007 (EXPRESS II)[379]	Infliximab 5 mg/kg infusion at week 0, 2 and 6	314	0	14
	Placebo infusion at week 0, 2 and 6	207	0	
Yang et.al., 2012[380]	Infliximab 5 mg/kg IV. drip infusion week 0, 2 and 6	84	0	10
	Placebo IV. drip infusion week 0, 2 and 6	45	0	
Infliximab vs methotrexate				
Barker et.al., 2011 (RESTORE1)[261]	Infliximab 5 mg/kg at weeks 0, 2, 6, 14 and 22	649	0	16
	Methotrexate 15 mg weekly with a dose increase to 20 mg weekly at week 6 if PASI < 25%	211	0	

Authors, year	Interventions	Number of participants receiving treatment	MACEs	Randomised controlled-phase (weeks)
Ixekizumab vs placebo				
Gordon et.al., 2016 (UNCOVER-1)[397]	Ixekizumab 160 mg SC. week 0 then 80 mg SC. every 2 weeks	433	0	12
	Placebo SC week 0 then every 2 weeks	431	0	
Secukinumab 150 mg vs secukinumab 300 mg				
Mrowietz et.al., 2015 (SCULPTURE)[381]	Secukinumab 150 mg SC. at week 0, 1, 2, 3, 4 and 8	482	0	12
	Secukinumab 300 mg SC. at week 0, 1, 2, 3, 4 and 8	483	1	
Secukinumab 150 mg vs secukinumab 300 mg vs placebo				
Langley et.al., 2014 (ERASURE)[382]	Secukinumab 150 mg SC. at week 0, 1, 2, 3, 4 and then every 4 weeks	245	0	12
	Secukinumab 300 mg SC. at week 0, 1, 2, 3, 4 and then every 4 weeks	245	0	
	Placebo at week 0, 1, 2, 3, 4 and then every 4 weeks	247	0	
Blauvelt et.al., 2015 (FEATURE)[383]	Secukinumab 150 mg SC. week 0, 1, 2, 3, 4 and 8	59	0	12
	Secukinumab 300 mg SC. week 0, 1, 2, 3, 4 and 8	59	2	
	Placebo SC. week 0, 1, 2, 3, 4 and 8	59	0	
Paul et.al., 2015 (JUNCTURE)[384]	Secukinumab 150 mg SC. week 0, 1, 2, 3, 4 and 8	61	0	12
	Secukinumab 300 mg SC. week 0, 1, 2, 3, 4 and 8	60	0	
	Placebo SC. week 0, 1, 2, 3, 4 and 8	61	0	
Ustekinumab vs placebo				
Tsai et.al., 2011 (PEARL)[385]	Ustekinumab 45 mg SC. at week 0 and 4	61	0	12
	Placebo SC. at week 0 and 4	60	0	
Zhu et.al., 2013 (LOTUS) [386]	Ustekinumab 45 mg SC. at week 0 and 4	160	0	12
	Placebo SC. at week 0 and 4	161	0	
Lebwohl et.al., 2015 (AMAGINE 2)[387]	Ustekinumab SC. (45 mg for patients with a body weight ≤ 100 kg and 90 mg for patients with a body weight > 100 kg) on day 1 and week 4	300	0	12
	Placebo	309	0	
Lebwohl et.al., 2015 (AMAGINE 3)[387]	Ustekinumab SC. (45 mg for patients with a body weight ≤ 100 kg and 90 mg for patients with a body weight > 100 kg) on day 1 and week 4	313	0	12
	Placebo	315	0	
Ustekinumab 45 mg vs ustekinumab 90 mg vs placebo				
Leonardi et.al., 2008 (PHOENIX 1)[391]	Ustekinumab 45 mg SC. at week 0 and 4	255	1	12
	Ustekinumab 90 mg SC. at week 0 and 4	255	0	
	Placebo at week 0 and 4	255	0	

Authors, year	Interventions	Number of participants receiving treatment	MACEs	Randomised controlled-phase (weeks)
Papp et.al., 2008 (PHOENIX 2)[388]	Ustekinumab 45 mg SC. at week 0 and 4	409	0	12
	Ustekinumab 90 mg SC. at week 0 and 4	411	1	
	Placebo	410	0	
Igarashi et.al, 2012[390]	Ustekinumab 45 mg SC. at week 0 and 4	64	0	12
	Ustekinumab 90 mg SC.at week 0 and 4	62	0	
	Placebo SC. at week 0 and 4	32	0	
Etanercept vs ustekinumab 45 mg vs ustekinumab 90 mg				
Griffiths et.al., 2010 (ACCEPT) [392]	Etanercept 50 mg SC. BIW	347	0	12
	Ustekinumab 45 mg SC. at week 0 and 4	209	0	
	Ustekinumab SC. 90 mg SC. at week 0 and 4	347	0	
Etanercept vs ustekinumab vs no treatment				
Merck Sharp & Dohme 2015, NCT01276847, ClinicalTrials.gov[393]	Etanercept 50 mg SC. BIW for 12 weeks then SC. QW for 4 weeks	10	0	16
	Ustekinumab 45 mg SC. for participants weighing ≤ 100 kg, and ustekinumab 90 mg SC. for participants weighing > 100 kg on day 1, and weeks 4 and 16	20	0	
	No treatment	10	0	
Etanercept vs secukinumab 150 mg vs seckinumab 300 mg vs placebo				
Langley et.al., 2014 (FIXTURE)[382]	Etanercept 50 mg SC. BIW	323	0	12
	Secukinumab 150 QW week 0, 1, 2, 3, 4 and then every 4 weeks	327	0	
	Secukinumab 300 QW week 0, 1, 2, 3, 4 and then every 4 weeks	326	0	
	Placebo at weeks corresponding to etanercept and secukinumab regimens	327	0	

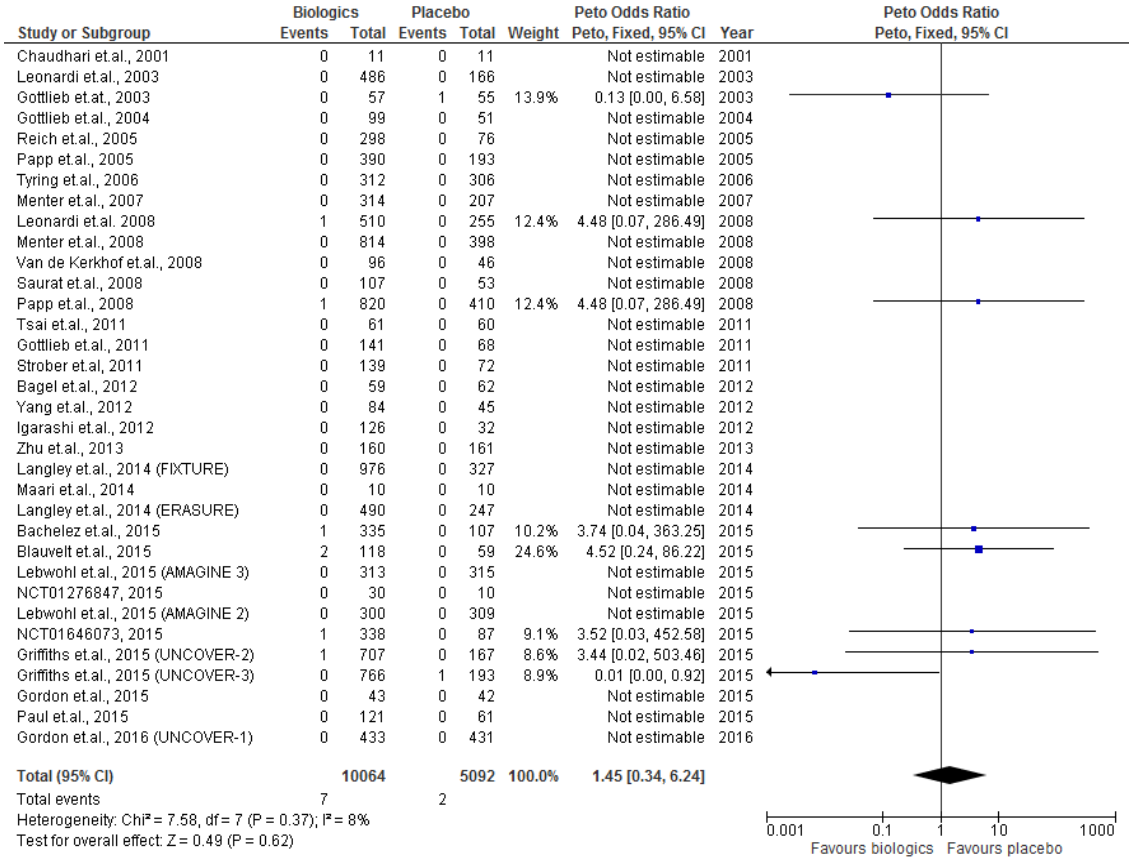
Abbreviations: BIW, twice weekly; EOW, every other week; IV., intravenous; MACEs, major adverse cardiovascular events; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; QW, once weekly; SC., subcutaneous

5.4.2 Meta-analysis

Patients in 27 RCTs[260,368–370,373–380,382,384–387,389,390,392,393,397,398,402,403] did not experience MACEs whilst exposed to any interventions but 10 MACEs were observed during the randomised controlled phase of nine studies.[371,372,381,383,388,391,399,401] Overall, the pooled analysis of these nine trials found that there was no statistically significant difference in the risk of MACEs when comparing biologic therapies with placebo (pooled OR 1.45, 95% CI 0.34 – 6.24, p = 0.62), as shown in Figure 5.2. There was very low levels of heterogeneity between the included RCTs [χ^2 = 7.58; degree of freedom (df) = 7; p = 0.37; I^2 = 8%].

Considered separately, there was also no statistically significant difference for patients receiving TNFi (adalimumab, etanercept and infliximab), anti-IL-17A agents (secukinumab and ixekizumab), or ustekinumab; the corresponding pooled ORs were 0.67, 95% CI 0.10 – 4.63, p = 0.69 for TNFi (Figure 5.3), 1.00, 95% CI 0.09 – 11.09, p = 1.00 for anti-IL-17A agents (Figure 5.4) and 4.48, 95% CI 0.24 – 84.77, p = 0.32 for ustekinumab (Figure 5.5). Comparing ustekinumab 45 mg against 90 mg and secukinumab 150 mg against 300 mg, the ORs suggest that there were no statistically significant differences in the risk of MACEs (OR 1.00, 95% CI 0.06 – 16.03, p = 1.00 in four ustekinumab trials (Figure 5.6) and OR 0.13, 95% CI 0.01 – 1.30, p = 0.08 in five secukinumab trials (Figure 5.7). The sensitivity analyses using the Mantel-Haenszel risk difference found similar results for all comparisons (as shown in Appendix 6).

Figure 5.2 Peto odds ratio of major adverse cardiovascular events and a funnel plot for the detection of publication bias in patients treated with biologic therapies versus placebo



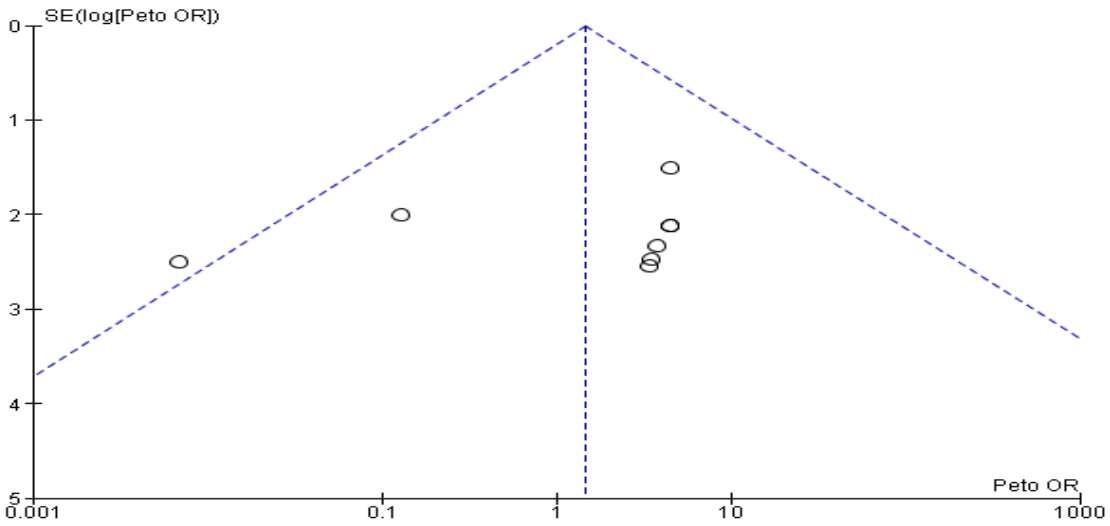
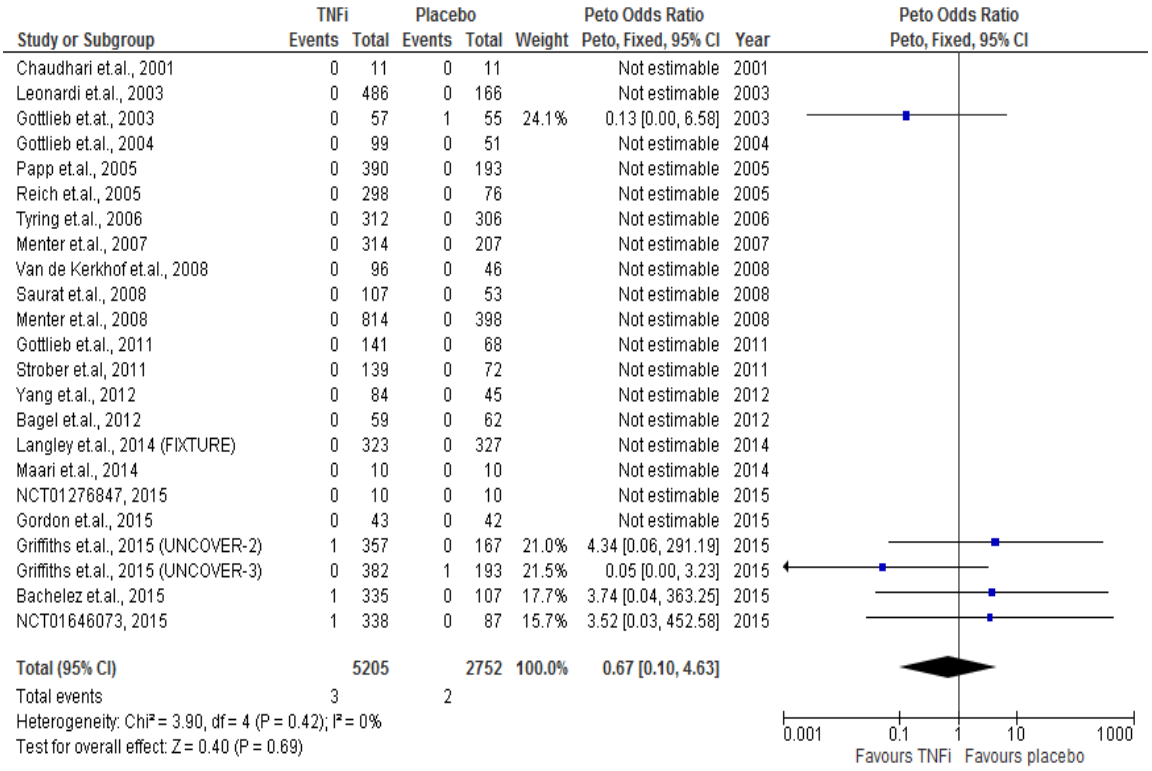


Figure 5.3 Peto odds ratio of major adverse cardiovascular events and a funnel plot for the detection of publication bias in patients treated with tumour necrosis factor-alpha inhibitors versus placebo



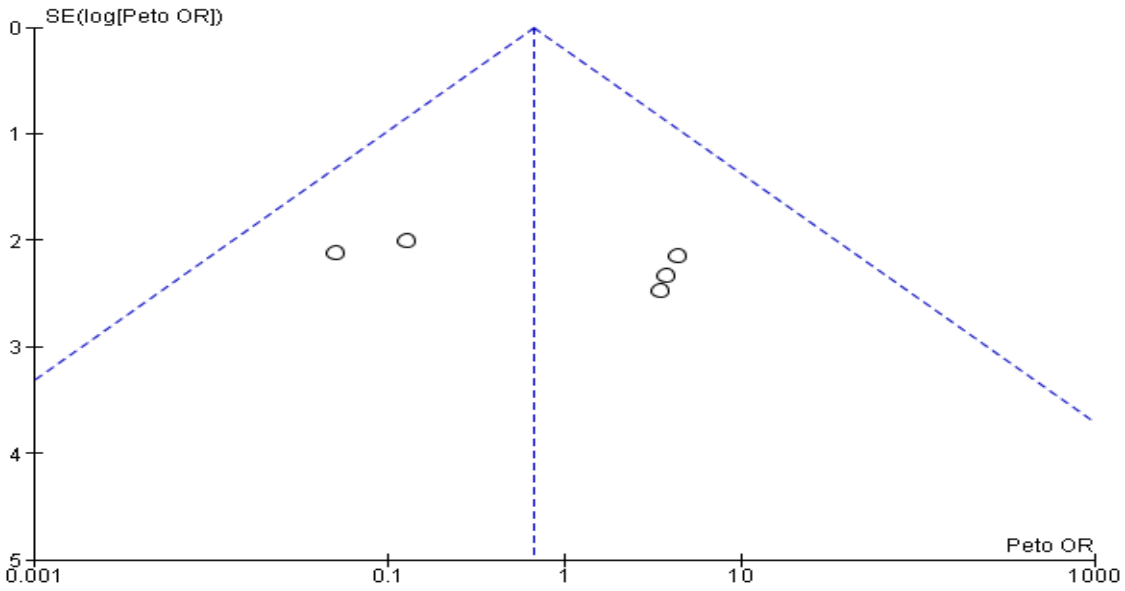


Figure 5.4 Peto odds ratio of major adverse cardiovascular events and a funnel plot for the detection of publication bias in patients treated with anti-interleukin-17A agents versus placebo

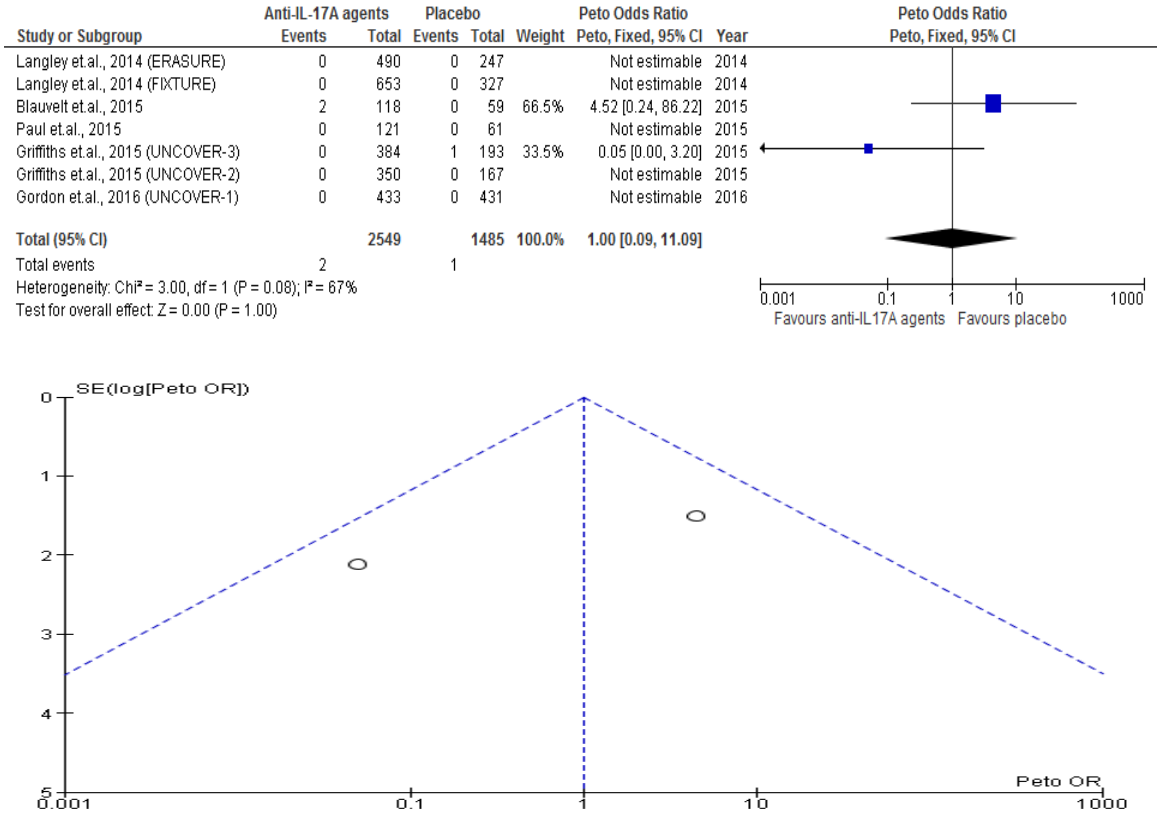
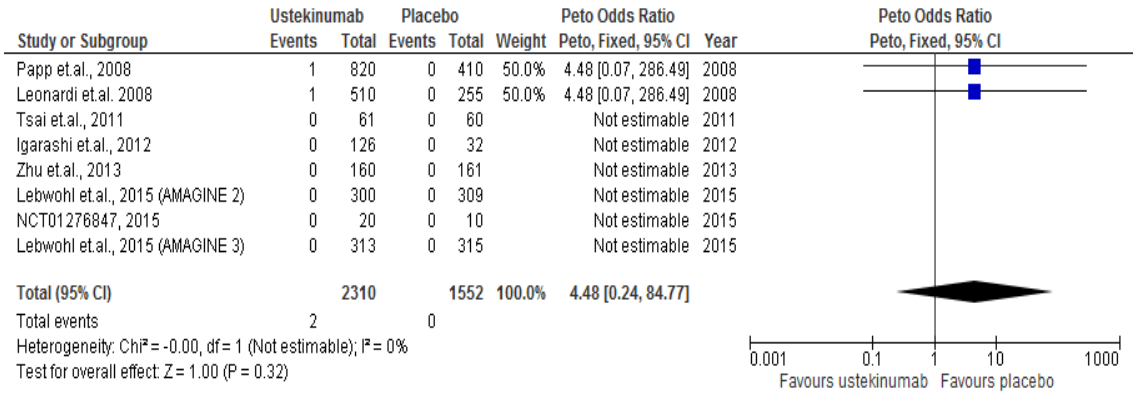


Figure 5.5 Peto odds ratio of major adverse cardiovascular events and a funnel plot for the detection of publication bias in patients treated with ustekinumab versus placebo



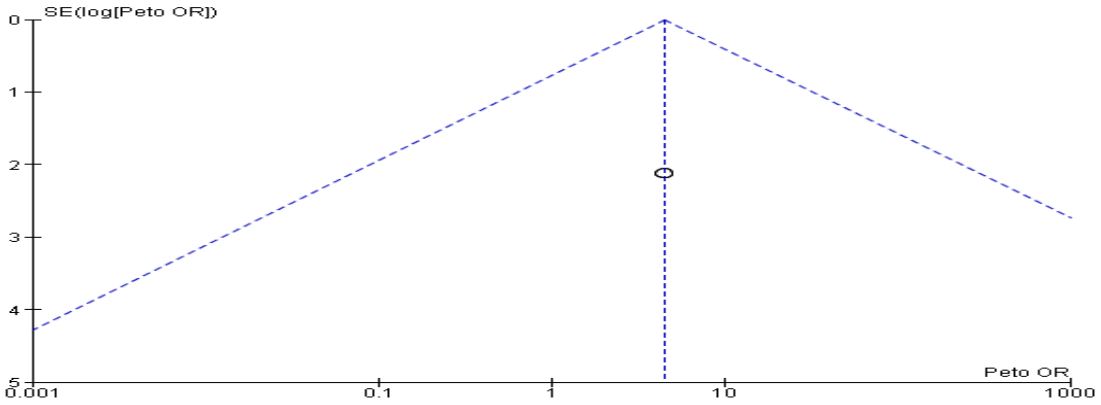
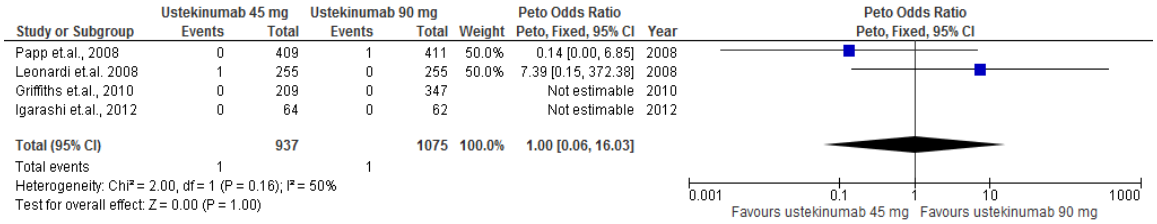


Figure 5.6 Peto odds ratio of major adverse cardiovascular events and a funnel plot for the detection of publication bias in patients treated with ustekinumab 45 mg versus 90 mg



Study or Subgroup	Ustekinumab 45 mg Events	Total	Ustekinumab 90 mg Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Papp et.al., 2008	0	409	1	411	50.0%	0.14 [0.00, 6.85]	2008
Leonardi et.al. 2008	1	255	0	255	50.0%	7.39 [0.15, 372.38]	2008
Griffiths et.al., 2010	0	209	0	347		Not estimable	2010
Igarashi et.al., 2012	0	64	0	62		Not estimable	2012
Total (95% CI)		**937**		**1075**	**100.0%**	**1.00 [0.06, 16.03]**	
Total events	1		1				

Heterogeneity: Chi² = 2.00, df = 1 (P = 0.16); I² = 50%
Test for overall effect: Z = 0.00 (P = 1.00)

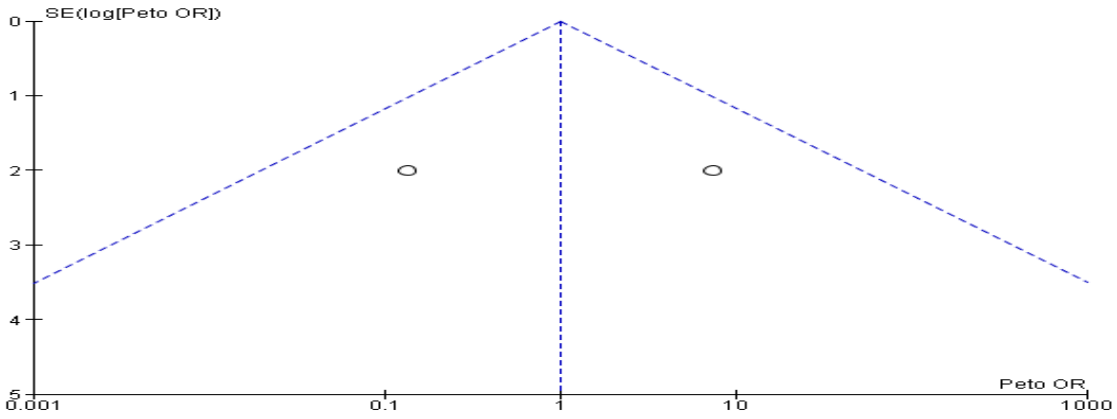
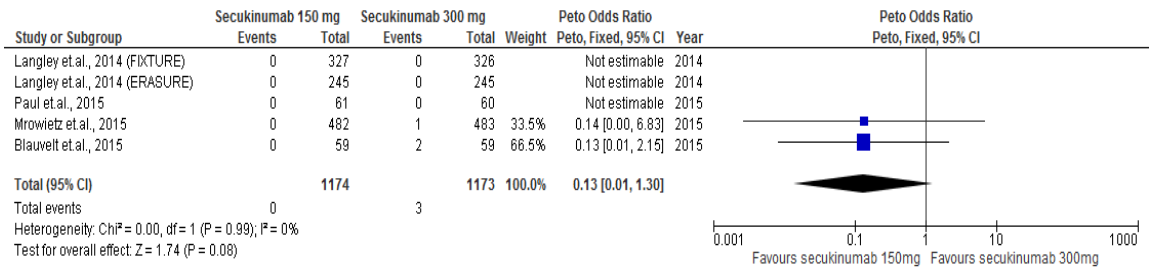
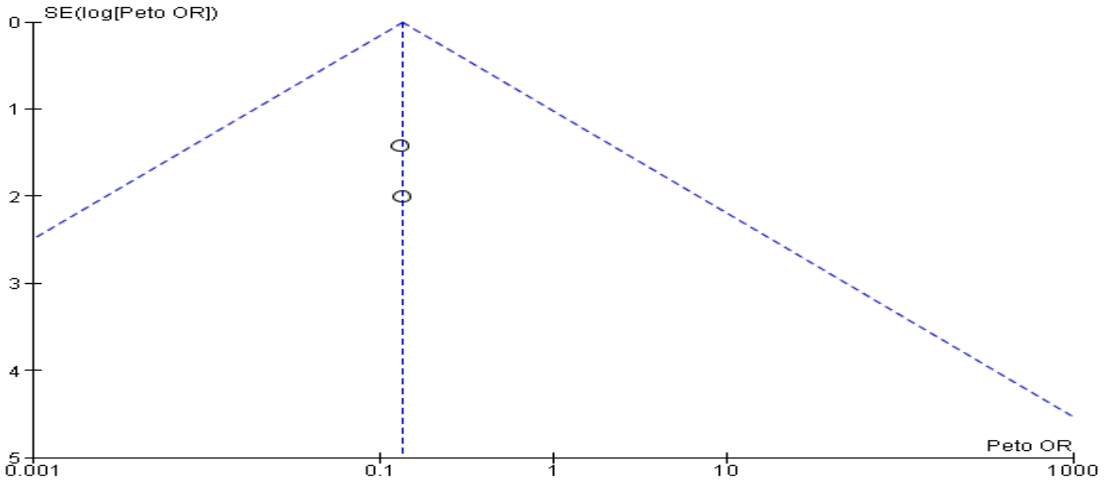


Figure 5.7 Peto odds ratio of major adverse cardiovascular events and a funnel plot for the detection of publication bias in patients treated with secukinumab 150 mg versus 300 mg



Study or Subgroup	Secukinumab 150 mg Events	Total	Secukinumab 300 mg Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Langley et.al., 2014 (FIXTURE)	0	327	0	326		Not estimable	2014
Langley et.al., 2014 (ERASURE)	0	245	0	245		Not estimable	2014
Paul et.al., 2015	0	61	0	60		Not estimable	2015
Mrowietz et.al., 2015	0	482	1	483	33.5%	0.14 [0.00, 6.83]	2015
Blauvelt et.al., 2015	0	59	2	59	66.5%	0.13 [0.01, 2.15]	2015
Total (95% CI)		**1174**		**1173**	**100.0%**	**0.13 [0.01, 1.30]**	
Total events	0		3				

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.74 (P = 0.08)



5.4.3 Risk of bias assessment

The risk of bias assessment found that 28 RCTs (73.7%; low risk of bias) adequately reported the generation of the random sequence, 27 RCTs (71.1%) adequately concealed allocation; 22 RCTs (57.9%) and 21 RCTs (55.3%) blinded patients and personnel, and outcome assessors respectively. Incomplete outcome data were well balanced in 33 RCTs (86.8%). Fifteen RCTs (39.5%) explicitly stated that CVEs were monitored and/or these outcomes were reported. Only 10 RCTs (26.3%) had a committee for adjudicating suspected MACEs. Among 36 RCTs (94.7%), patient characteristics in all intervention groups were well balanced (Table 5.3).

Table 5.3 Risk of bias assessment for the included randomised controlled trials

Authors, year	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Adjudicate of MACEs	Baseline imbalance
Adalimumab vs placebo								
Menter et.al., 2008 (REVEAL)[378]	Low	Low	Unclear	Low	Low	Unclear	Unclear	Low
Maari et.al., 2014[389]	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	Low
Gordon et.al., 2015 (X-PLORE)[398]	Unclear	Unclear	High	Unclear	Low	Unclear	Unclear	Low
NCT01646073, clinicaltrials.gov, 2015[399], AbbVie, 2014[400]	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
Adalimumab vs methotrexate								
Goldminz et.al., 2015[394]	Unclear	Unclear	High	Low	Low	Unclear	Unclear	Low
Adalimumab vs methotrexate vs placebo								
Saurat et.al., 2008 (CHAMPION)[260]	Low	Low	Low	Low	Low	Unclear	Unclear	Low
Etanercept vs placebo								
Gottlieb et.at., 2003[401]	Low	Low	Low	Low	High	Unclear	Unclear	Low
Tyring et.al., 2006[402]	Low	Low	Unclear	Unclear	Low	Low	Unclear	Low
van de Kerkhof et.al., 2008[403]	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	Low
Gottlieb et.al., 2011[368]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	Low
Strober et.al., 2011[369]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	Low
Bagel et.al., 2012[370]	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Bachelez et.al., 2015[371]	Low	Low	Low	Low	Low	Low	Low	Low
Etanercept (different strengths) vs placebo								
Leonardi et.al., 2003[373]	Low	Low	Low	Low	Unclear	Unclear	Unclear	Low
Papp et.al., 2005[374]	Low	Low	Low	Low	Low	Unclear	Unclear	Low
Etanercept vs ixekizumab vs placebo								
Griffiths et.al., 2015 (UNCOVER-2)[372]	Low	Low	Low	Unclear	Low	Low	Low	Low
Griffiths et.al., 2015 (UNCOVER-3)[372]	Low	Low	Low	Low	Low	Low	Low	Low
Infliximab vs placebo								
Chaudhari et.al., 2001[375]	Low	Low	Low	Low	Low	Unclear	Unclear	Low
Gottlieb et.al., 2004 (SPIRIT)[376]	Low	Low	Low	Unclear	High	Unclear	Unclear	Low
Reich et.al., 2005 (EXPRESS)[377]	Low	Low	Low	Low	Low	Unclear	Unclear	Low
Menter et.al., 2007 EXPRESS II)[379]	Low	Low	Low	Low	Low	Unclear	Unclear	Low
Yang et.al., 2012[380]	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
Infliximab vs methotrexate								
Barker et.al., 2011 (RESTORE1)[261]	Low	High	High	High	Unclear	Unclear	Unclear	Unclear
Ixekizumab vs placebo								
Gordon et.al., 2016 (UNCOVER-1)[397]	Low	Low	Low	Low	Low	Low	Low	Low
Secukinumab 150 mg vs secukinumab 300 mg								
Mrowietz et.al., 2015 (SCULPTURE)[381]	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	Low
Secukinumab 150 mg vs secukinumab 300 mg vs placebo								
Langley et.al., 2014 (ERASURE)[382]	Low	Low	Low	Low	Low	Low	Low	Low
Blauvelt et.al., 2015	Low	Low	Low	Low	Low	Low	Low	Low

Authors, year	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Adjudicate of MACEs	Baseline imbalance
(FEATURE)[383]								
Paul et.al., 2015 (JUNCTURE)[384]	Low	Low	Low	Low	Low	Low	Unclear	Low
Ustekinumab vs placebo								
Tsai et.al., 2011 (PEARL)[385]	Low	Low	Low	Unclear	Low	Unclear	Unclear	Low
Zhu et.al., 2013 (LOTUS)[386]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	Low
Lebwohl et.al.a., 2015 (AMAGINE 2)[387]	Low	Low	Low	Low	Low	Low	Low	Low
Lebwohl et.al.b., 2015 (AMAGINE 3)[387]	Low	Low	Low	Low	Low	Low	Low	Low
Ustekinumab 45 mg vs ustekinumab 90 mg vs placebo								
Leonardi et.al., 2008 (PHOENIX 1)[391]	Low	Low	Low	Low	Low	Unclear	Unclear	Low
Papp et.al., 2008 (PHOENIX 2)[388]	Low	Low	Low	Unclear	Low	Unclear	Unclear	Low
Igarashi et.al, 2012[390], NCT00723528, clinicaltrials.gov, 2014[395]	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
Etanercept vs ustekinumab 45 mg vs ustekinumab 90 mg								
Griffiths et.al., 2010 (ACCEPT)[392]	Low	Low	Unclear	Low	Low	Low	Low	Low
Etanercept vs ustekinumab vs no treatment								
Merck Sharp & Dohme 2015, NCT01276847, clinicaltrials.gov[393]	Unclear	High	High	High	Low	Unclear	Unclear	Unclear
Etanercept vs secukinumab 150 mg vs secukinumab 300 mg vs placebo								
Langley et.al., 2014 (FIXTURE)[382]	Low	Low	Low	Low	Low	Low	Low	Low

Abbreviation: MACEs, major adverse cardiovascular events

Funnel plot analysis using the Peto method was used for assessing potential publication bias and visual inspection of funnel plot for the outcomes in TNFi studies did not show any evidence of publication bias (Figure 5.3). For the Mantel-Haenszel fixed-effect method, funnel plot analysis also did not show evidence of publication bias in all comparisons (Appendix 6).

5.5 Discussion

This meta-analysis of RCTs found that there was no statistically significant difference in the risk of MACEs in patients with plaque psoriasis exposed to biologic therapies (adalimumab, etanercept, infliximab, ustekinumab, secukinumab and ixekizumab) used at the licensed doses compared to placebo. Moreover, no difference in the risk was also found for comparisons between different licensed doses of ustekinumab (45 mg vs 90 mg) or secukinumab (150 mg vs 300 mg).

Two earlier meta-analyses of RCTs have examined the risk of MACEs and biologic therapies for the treatment of psoriasis. The first included 22 trials and reported that TNFi (adalimumab, etanercept and infliximab) and anti-IL-12/23 agents (ustekinumab and briakinumab) were not associated with an increased risk of MACEs.[336] This meta-analysis used a Mantel-Haenszel

fixed-effect model to examine absolute risk difference, which is generally considered a less appropriate method for detecting rare events (lower than 1%).[366] Risk difference meta-analytical method produces estimates for all included studies owing to using 0.5 zero-cell corrections. The corrections are used when the included studies with no events are found in any arms. Risk difference meta-analytical method tends to show conservative CI coverage and low statistical power when the events are rare.[366] Peto OR method which removes studies without events from an analysis is reported that it is the least biased and most powerful method for rare events when compared with other meta-analytical methods. It produces the best CI coverage.[366] Due to the exclusion of studies without events, it may lead to an overestimation of true relative risk.[404]

The second meta-analysis included 9 trials to examine the association between MACEs and anti-IL-12/23 agents (ustekinumab and briakinumab).[337] The results of this analysis suggested that anti-IL-12/23 agents were significantly associated with an increased risk of MACEs. In the meta-analysis presented in this thesis, briakinumab was not included as this has not been licensed for use by the regulatory agencies. However, newer licensed biologic therapies (secukinumab and ixekizumab) were included. One important limitation of the earlier meta-analyses is that they included patients treated with both non-licensed and licensed doses of biologic therapies whilst this meta-analysis has focussed only on those patients receiving biologic therapies at licensed dose regimens.

Nonetheless, this meta-analysis was still faced with an important limitation. Most included RCTs had a small sample size and a short duration of the randomised controlled phase of the treatment (ranging from 10 to 30 weeks). These factors would impact on the power of the included studies to detect a change in the risk of MACEs and this uncertainty was reflected by the wide CIs surrounding some of this risk estimates. Moreover, the included RCTs tended to include patients with fewer comorbidities than those seen in clinical practice. It may limit the generalisability of the findings. Therefore, well-designed prospective cohort studies are needed which involve larger numbers of patients and longer durations of treatment exposure reflecting routine clinical practice in order to better examine the impact of biologic therapies on the risk of CVEs in patients with psoriasis. The next chapter will present the results of a prospective cohort study examining this association using a BADBIR dataset.

Chapter 6

Risk of major cardiovascular events in patients with psoriasis receiving biologic therapies: prospective cohort study

6.1 Introduction

Chapter 5 presented the findings from a systematic review and meta-analysis of RCTs in adult patients with plaque psoriasis exposed to biologic therapies. It showed that there were no significant differences in the risk of MACEs in patients with plaque psoriasis, although there were some important limitations of the included RCTs. Specifically, the trials had short durations of exposure and relatively small sample sizes. In addition, patients in RCTs tended to have fewer comorbidities than those seen in real-life practice. As mentioned in Chapter 2, earlier cohort studies examining the relationship between CVEs and biologic therapies in patients with psoriasis had some important limitations. They used inappropriate reference groups which included non-biologic therapies, non-systemic therapies (topical therapy, phototherapy and climate therapy) or methotrexate.[7–11] These therapies are generally recommended for patients before receiving biologic therapies. Therefore, patients with milder severity of psoriasis which have different risk levels for the development of CVEs[220] tended to receive these therapies compared with psoriasis patients receiving biologic therapies. Since participants in both comparison groups had the different risk levels for the development of CVEs, it could bias the results of these cohort studies. Large cohort studies which directly compare biologic therapies are required to examine the impact of these therapies on the risk of major CVEs in patients with psoriasis. This chapter describes the results of a prospective cohort study examining the relationship between biologic therapies and major CVEs using the BADBIR dataset.

6.2 Aim and objectives

This chapter aimed to assess the association between biologic therapies and major CVEs in patients with psoriasis in a prospective cohort study.

The objectives of this study were:

- To compare baseline characteristics of adult patients with plaque psoriasis receiving biologic therapies and methotrexate
- To calculate the incidence rates, incidence rate ratios and HRs for the risk of major CVEs in adult plaque psoriasis patients treated with biologic therapies or methotrexate

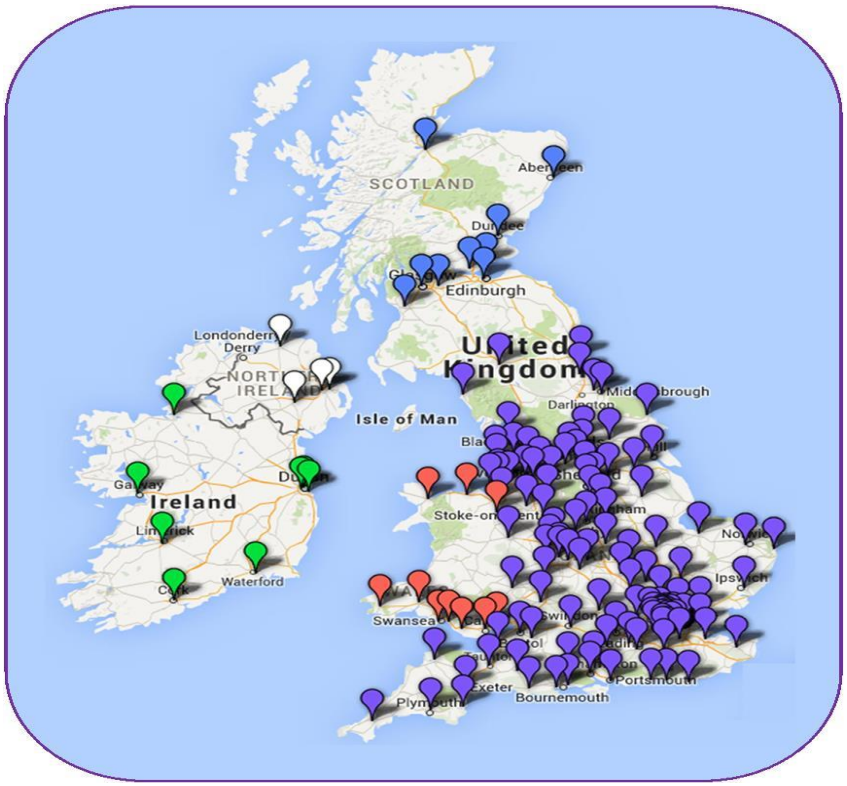
6.3 Methods

6.3.1 BADBIR Database

The BADBIR is a large prospective observational pharmacovigilance registry in the UK and Republic of Ireland. It was established in September 2007 with the primary aim to examine the long-term safety profile of biologic therapies for the treatment of psoriasis. It has enrolled three psoriasis cohorts. The first cohort recruits patients receiving a biologic therapy while the second cohort recruits patients receiving only conventional systemic therapies (e.g. methotrexate).[12] Patients who receive a non-biologic small molecule (i.e. apremilast and dimethyl fumarate) are

recruited in the third cohort. UK guidelines and the NICE recommend psoriasis patients treated with a biologic therapy should be enrolled in this registry.[45,330] Currently, the BADBIR recruits psoriasis patients from 157 secondary care dermatology centres across the UK and Republic of Ireland (Figure 6.1).

Figure 6.1 BADBIR study sites



Multicentre research ethics committee approval for the BADBIR was obtained in March 2007 (National Health Service Research Ethics Committee North West England, 07/MRE08/9) and local research ethical committee approval was also obtained at each recruiting site (Appendix 7) Patients who participate in this registry have to read the study information sheet (Appendix 8) and sign the consent form (Appendix 9).

The BADBIR is coordinated by the University of Manchester, and funded by the BAD. The BAD receives income from pharmaceutical companies marketing biologic therapies for the treatment of psoriasis. This income finances a separate contract between the BAD and the University of Manchester. Researchers who work on this database have academic freedom without pharmaceutical influence.

6.3.2 Participants in the BADBIR

The BADBIR recruits psoriasis patients who meet the inclusion criteria outlined in Table 6.1. Psoriasis patients are offered a biologic therapy when their conditions meet the requirements of guidelines from the UK, Scotland or Republic of Ireland.[45,51,330] However, the BADBIR has not

defined these criteria (e.g. PASI and DLQI) for psoriasis patients in the biologic cohort and the non-biologic small molecule cohort.

Table 6.1 Inclusion criteria for the BADBIR

	Biologic cohort	**Conventional systemic cohort**	**Non-biologic small molecule cohort**
Diagnosis by a dermatologist	Psoriasis	Psoriasis	Psoriasis
Therapy	Start on or switch to a biologic therapy (i.e. efalizumab, adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekinumab and certolizumab) within previous 6 months of registration **Note:** 1) Since efalizumab was withdrawn, patients receiving this biologic therapy were recruited until 2009. 2) Patients receiving infliximab have not been recruited since 31st July 2013.	Start on or switch to a conventional systemic therapy (i.e. methotrexate, ciclosporin, acitretin, fumaric acide esters, hydroxycarbamide and PUVA) within previous 6 months of registration	Start on or switched to a non-biologic small molecule therapy (i.e. apremilast and dimethyl fumarate) within previous 6 months of registration
Other factors	**-**	PASI ≥ 10 and DLQI > 10 (except switching between conventional systemic therapies)	-
	-	Never exposed to a biologic therapy	Never exposed to a biologic therapy

Abbreviations: BADBIR, British Association of Dermatologists Biologic Interventions Register; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PUVA, psoralen and ultraviolet A

6.3.3 Data collection

Baseline assessments

Baseline data collected at enrolment includes patient demographic characteristics, comorbidities, anthropometric data, drug therapies and clinical data such as type and severity of psoriasis (PASI) by health care professionals using an online database while lifestyle information such as smoking and alcohol consumption are collected directly from patients using a questionnaire (Appendix 10).

Follow-up assessments

Patients recruited into the BADBIR are followed up as long as they are in the register. Data are collected every 6 months for the first 3 years and then every year thereafter. This includes information on changes to drug therapies, measures of disease severity, hospitalisation and details of AEs including the outcomes of interest of this study (Appendix 11). Patient death details are derived from the BADBIR register and the ONS mortality records. AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) system.[405]

After these data are received, the BADBIR team routinely check the quality of data involving manual data cleaning to examine every record against the eligibility criteria. If any discrepancies are found, the BADBIR team will send queries to the study sites for clarification.

6.3.4 Study design

Study population and exposure

Patients who enrolled in the BADBIR from September 2007 – October 2016 and had at least six months of follow-up data following initiation of treatment were selected for this study. Biologic-naïve patients aged at least 18 years old with chronic plaque psoriasis who had no prior history of major CVEs were selected for the inclusion in this cohort study. For the main analysis, patients receiving first-line originator anti-IL-12/23 agent (ustekinumab) were compared with TNFi (etanercept or adalimumab) as the reference group. For the secondary analyses, patients receiving first-line adalimumab (the referent group) were compared with ustekinumab, etanercept or methotrexate. This study did not include infliximab due to the small sample size and it was reserved to use in patients with more severe psoriasis than patients receiving other biologic therapies in the UK.

Outcome of interest and ascertainment

The outcome of interest was fatal or non-fatal major CVEs (acute coronary syndrome, unstable angina, MI or stroke). The list of MedDRA codes regarding major CVEs was identified and discussed by W.R., M.K.R. and D.M.A. Table 6.2 provides the relevant MedDRA outcome codes. Death codes were reviewed with other terms in order to identify fatal major CVEs. All relevant MedDRA codes or descriptions of events were identified by W.R. Both codes and descriptions were reviewed in order to ascertain the outcome of the study by W.R. and M.K.R.

as an expert in cardiovascular studies. Some relevant MedDRA codes in the BADBIR dataset were recorded incorrectly and some major CVEs were recorded in only the descriptions of events but not recorded by MedDRA codes. W.R. asked for clarification about these cases from K.M. (as part of the BADBIR management team). When K.M. clarified these suspected cases and agreed that they might be the outcome of interest for this study, W.R. and D.M.A. made decisions whether these suspected events should be included in this study.

Table 6.2 Potential adverse event terms

System organ class (MedDRA system organ class)	AE preferred term (MedDRA preferred term)
Cardiac disorders	Acute coronary syndrome
	Acute myocardial infarction
	Angina unstable
	Myocardial infarction
General disorders and administration site conditions	Death
Nervous system disorders	Carotid artery occlusion
	Cerebellar haemorrhage
	Cerebral haemorrhage
	Cerebral infarction
	Cerebrovascular accident
	Intracranial haemorrhage
	Hemiparesis
	Hemiplegia
	Ischaemic stroke
	Lacunar infarction
	Monoplegia
	Subarachnoid haemorrhage
	Subdural haematoma
	Thalamic infarction

Abbreviations: AE, adverse event; MedDRA, Medication Dictionary for Regulatory Activities

Data analysis

Patients were observed from the date of receiving therapy to developing the first major CVE; the earliest date of change of treatment (changing to other biologic therapy in the biologic cohorts or starting a biologic therapy in the methotrexate cohort); end of recorded data in the BADBIR; death; or end of the study follow-up (30th September 2016). Discontinuation of treatment was defined as a gap in a regimen for more than 90 days. The risk of major CVEs was examined over two periods: 1) whilst exposed to treatment and 2) extending the exposure effect window until 90 days after the last dose. Planned secondary analyses included direct comparisons between the individual biologic therapies and users of methotrexate.

Descriptive statistics were used to analyse baseline patient characteristics. Frequency (%) and median values (p25 - p75) were calculated for categorical and continuous variables, respectively. To control for imbalances in patient characteristics between cohorts, propensity score technique was used. This statistical technique is designed to balance the comparison groups on all measured covariates so that it mimics a randomised trial.[406] Propensity score technique can balance several covariates using a score calculated for each patient while multiple regression adjustment requires 10 events/an adjusted covariate[407]. Since the outcome of this study (major CVEs) was a rare event and multiple cardiovascular risk factors had to be controlled for, this technique was used for this study. An exposure-specific propensity score which was calculated was based on the predicted probability of receiving the treatment of interest conditional upon the subjects' baseline covariates using logistic regression models for the primary analysis and multinomial logistic regression models for the sensitivity analyses. The covariates were considered to be included the models if they were strongly related to the outcome; or the outcome and the exposure. These could reduce the variance of estimated exposure effects but not increase the bias.[408] Covariates which were associated with only the exposures would not be included in the models since they could not decrease bias but they increased the variance of the estimates.[408] The models included the following covariates: baseline PASI (the score which was before and closest to the start of the treatment exposures within 6 months), smoking status (ever/never), current alcohol drinking (yes/no), alcohol consumption (units/week), obesity (≥30 kg/m^2), age, sex, history of psoriatic arthritis, hypertension, diabetes, dyslipidaemia, previous treatment with ciclosporin, acitretin, fumaric acid esters and methotrexate. After generating propensity scores, these scores were used by overlap weighting method. It could minimise the asymptotic variance of the weighted average treatment effects in the distribution of covariates between comparison groups.[409] Overlap weights which were proportional to the probability of patients being assigned to the reference groups were calculated for only patients having predicted probabilities within the common support range. The common support range was defined as propensity scores of the treated groups overlapping the propensity scores of the reference groups. Covariate balance between the cohorts before and after propensity score overlap weighting was assessed using the expected percentage bias which is the difference in the outcome owing to the imbalance between each covariate taking into account the strength of the association between each covariate and the outcome. A maximum bias of 5% in either direction was considered an acceptable threshold.

Multiple imputation was used to address missing data for baseline PASI score, smoking status, current alcohol drinking, alcohol consumption and obesity using chained equations of 20 cycles to reduce bias. This method preserved the variability and uncertainty of missing data and avoids the loss of power and bias when compared with complete case analysis.[410] The imputation model consisted of exposures, start year of exposure, log of censoring time for the outcome occurring during drug therapy; and during the extended window period, and whether patients experienced the outcomes during drug therapy; and during the extended window period, concomitant drug therapies including ciclosporin, acitretin, fumaric acid esters and

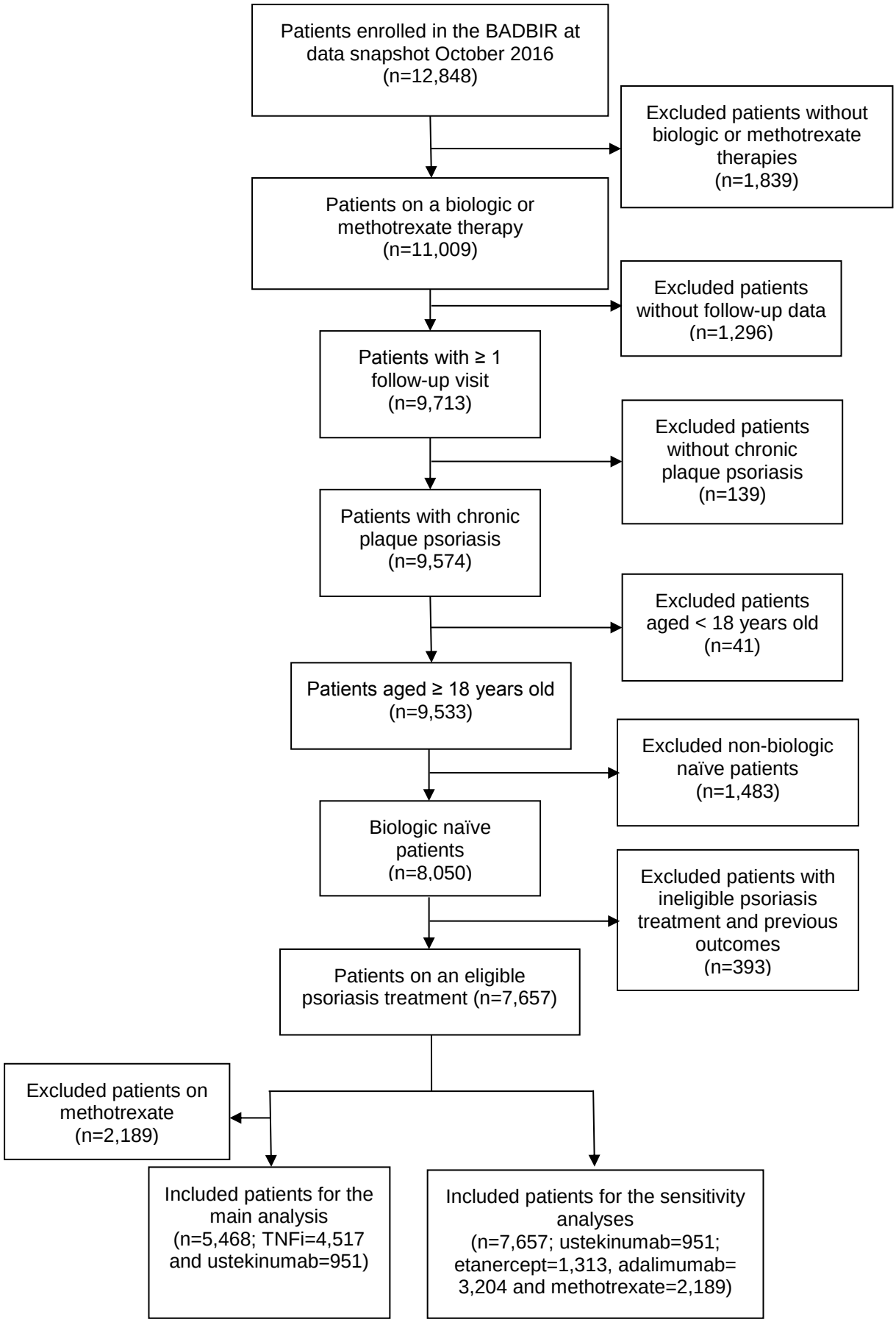
methotrexate; and the other covariates included in the propensity score models for the main analysis whilst the sensitivity analyses did not include concomitant methotrexate.

For each comparison (ustekinumab vs TNFi for the primary analysis; and ustekinumab, etanercept or methotrexate vs adalimumab for the secondary analyses) and for all outcomes, incidence rates, incidence rate ratios, unadjusted, age and sex adjusted and overlap weighed HRs with 95% CIs were calculated. The proportional hazards assumption was assessed by examining Schoenfeld residuals, and confirming that it was not violated. All analyses were performed using Stata 14 (StataCorp LP, College Station, Texas, USA).

6.4 Results

A total of 5,468 patients were included in the main analysis [anti-IL -12/23 agent (ustekinumab): 951 and TNFi (adalimumab and etanercept): 4,517] (Figure 6.2). Patients in the ustekinumab group were more likely to be obese, but less likely to have either a history of psoriatic arthritis, currently drink alcohol or concomitantly receive methotrexate therapy, as shown in Table 6.3. The median (p25 - p75) follow-up times for patients taking individual therapies were: ustekinumab 1.76 (0.92 – 2.96) years and TNFi 1.69 (0.81 – 3.10) years for the analysis of events occurring during drug therapy; and ustekinumab 2.01 (1.16 – 3.21) years and TNFi 1.93 (1.05 – 3.34) years for the analysis of events occurring during the extended exposure window period.

Figure 6.2 Patient selection



Abbreviations: BADBIR, British Association of Dermatologists Biologic Interventions Register; TNFi, tumour necrosis factor-alpha inhibitors

Table 6.3 Baseline characteristics of patients receiving anti-interleukin-12/23 agent (ustekinumab) and tumour necrosis factor-alpha inhibitors

Characteristics	Ustekinumab	TNFi
Number of patients (N=5,468)	951	4,517
Age (years) (N=5,468)	45 (35 - 54)	44 (35.2 - 53)
	(n=951)	(n=4,517)
Sex, male (N=5,468)	590 (62.0)	2,645 (58.6)
	(n=951)	(n=4,517)
Ethnicity, white (N=5,461)	853 (89.7)	4,157 (92.2)
	(n=951)	(n=4,510)
BMI (kg/m^2) (N=4,983)	30.3 (26.2 – 35.7)	29.4 (25.9 – 33.8)
	(n=851)	(n=4,132)
Obese (BMI≥30kg/m^2)	441 (51.8)	1,922 (46.5)
	(n=851)	(n=4,132)
Ever smoke (yes/no) (N=4,885)	599 (66.6)	2,541 (63.8)
	(n=899)	(n=3,986)
Disease durations (years) (N=5,417)	19 (11 - 30)	20 (12 - 29)
	(n=943)	(n=4,474)
PASI score (N=4,833)	14.6 (11.2 – 19.2)	14.1 (11.0 – 19.3)
	(n=845)	(n=3,988)
DLQI (N=2,949)	18 (12 - 24)	18 (13 - 24)
	(n=460)	(n=2,489)
Comorbidities (N=5,468)		
No comorbidities	315 (33.1)	1,356 (30.0)
Psoriatic arthritis	134 (14.1)	1,035 (22.9)
Hypertension	241 (25.3)	1,103 (24.4)
Diabetes mellitus	98 (10.3)	357 (7.9)
Dyslipidaemia	98 (10.3)	435 (9.6)
Other comorbidities	513 (53.9)	2,430 (53.8)
Current alcohol drinking (N=4,899)	593 (65.7)	2,854 (71.4)
	(n=903)	(n=3,996)
Alcohol units per week in patients consuming	8 (3 - 15)	9 (3 - 16)
alcohol (N=3,382)	(n=584)	(n=2,798)
Previous treatment of conventional systemic therapies		
Methotrexate	667 (70.1)	3,124 (69.2)
Ciclosporin	540 (56.8)	2,585 (57.2)
Acitretin	399 (42.0)	2,008 (44.5)
Fumaric acid esters	165 (17.4)	879 (19.5)
Concomitant therapies during drug therapy		
Methotrexate	120 (12.6)	909 (20.1)
Ciclosporin	71 (7.5)	455 (10.1)

Characteristics	Ustekinumab	TNFi
Acitretin	28 (2.9)	163 (3.6)
Fumaric acid esters	13 (1.4)	79 (1.8)
Concomitant therapies during drug therapy or window period (90 days)		
Methotrexate	121 (12.7)	946 (20.9)
Ciclosporin	74 (7.8)	491 (10.9)
Acitretin	29 (3.1)	179 (4.0)
Fumaric acid esters	13 (1.4)	87 (1.9)

Data are n (%) or median (25th percentile - 75th percentile)

Abbreviations: BMI, body mass index; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area Severity Index; TNFi, tumour necrosis factor-alpha inhibitors

Seven patients in the ustekinumab group experienced a major CVE during treatment with no additional patients experiencing such an outcome within 90 days after the last dose. For the TNFi cohort, 24 and 29 patients experienced major CVEs during drug therapy and during the extended exposure window period, respectively. The median times to onset of the major CVEs in both groups were about 1 year during either drug therapy or the extended exposure window period (Table 6.4).

Incidence rates of major cardiovascular events

The incidence rates of major CVEs associated with ustekinumab therapy for both periods were numerically but not statistically significantly higher than those associated with TNFi. Crude incidence rates (95% CI) in the ustekinumab and TNFi groups were 3.61 (1.72 – 7.58) and 2.46 (1.65 – 3.67) per 1,000 patient-years, respectively for the outcome during drug therapy; and 3.23 (1.54 – 6.77) and 2.67 (1.86 – 3.84) per 1,000 patient-years, respectively for the extended exposure window period (Table 6.4).

Table 6.4 Incidence rates and incidence rate ratios among patients receiving anti-interleukin-12/23 agent (ustekinumab) and tumour necrosis factor-alpha inhibitors

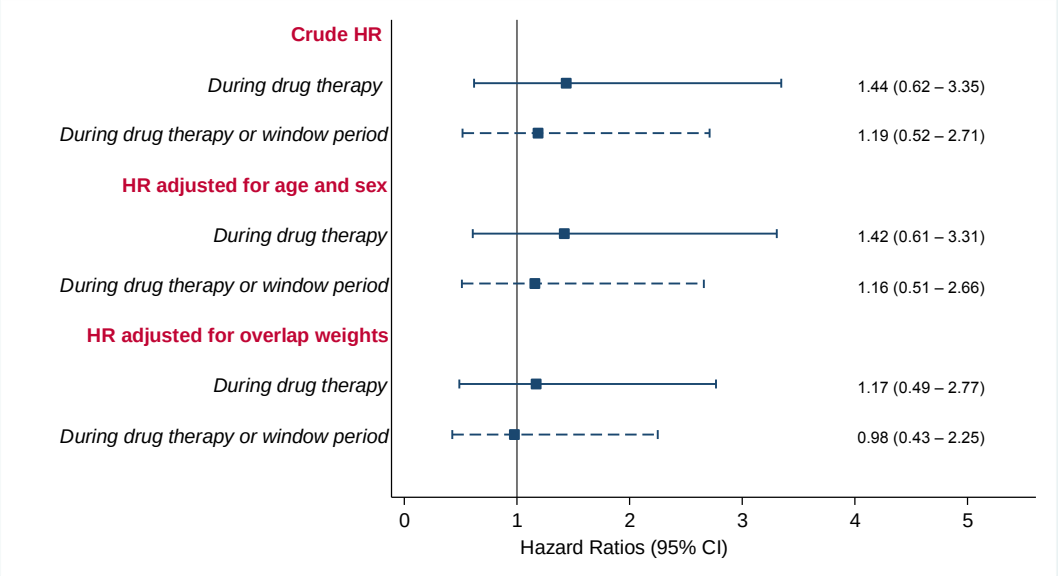
	Ustekinumab	TNFi
Outcome during drug therapy		
Total patient-years	1,936.56	9,757.22
Patient-years of follow-up (median, p25-p75)	1.76 (0.92 – 2.96)	1.69 (0.81 – 3.10)
Number of major cardiovascular events	7	24
Incidence rate per 1,000 patient-years (95% CI)	3.61 (1.72 – 7.58)	2.46 (1.65 – 3.67)
Incidence rate ratio	1.47 (0.53 - 3.52)	Reference
Duration between the start of exposure to development of the outcome (years) (median, p25-p75) (only patients experiencing the outcome)	1.06 (0.59 – 1.94)	1.19 (0.50 – 2.14)
Outcome during drug therapy or window period (90 days)		
Total patient-years	2,167.61	10,858.90
Patient-years of follow-up (median, p25-p75)	2.01 (1.16 – 3.21)	1.93 (1.05 – 3.34)
Number of major cardiovascular events	7	29
Incidence rate per 1,000 patient-years (95% CI)	3.23 (1.54 – 6.77)	2.67 (1.86 – 3.84)
Incidence rate ratio	1.21 (0.45 – 2.82)	Reference
Duration between start of exposure to development of the outcome (years) (median, p25-p75) (only patients experiencing the outcome)	1.06 (0.59 – 1.94)	1.06 (0.47 – 1.98)

Abbreviations: CI, 95% confidence interval; p25 - p75, 25th percentile - 75th percentile; 95%; TNFi, tumour necrosis factor-alpha inhibitors

Comparative risks of major cardiovascular events

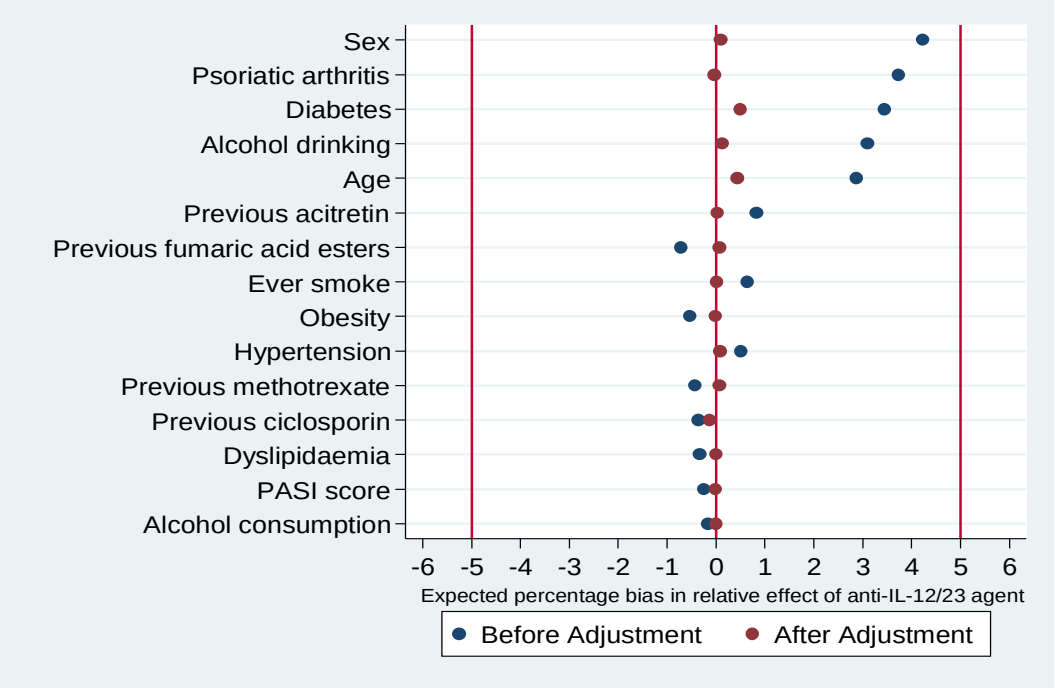
The unadjusted and age-sex adjusted HRs showed no difference in the risk of major CVEs between patients treated with ustekinumab and TNFi therapies. In the propensity score adjusted analysis, there was similarly no difference in the risk of major CVEs occurring during both periods (Figure 6.3). The baseline characteristics of the treatment cohorts were comparable after applying the overlap weights using the propensity score method as shown in Figure 6.4 – 6.5.

Figure 6.3 Crude and adjusted hazard ratios (95% confidence interval) for major cardiovascular events associated with different psoriasis therapies for a comparison of anti-interleukin-12/23 agent (ustekinumab) with tumour necrosis factor-alpha inhibitors (referent group)



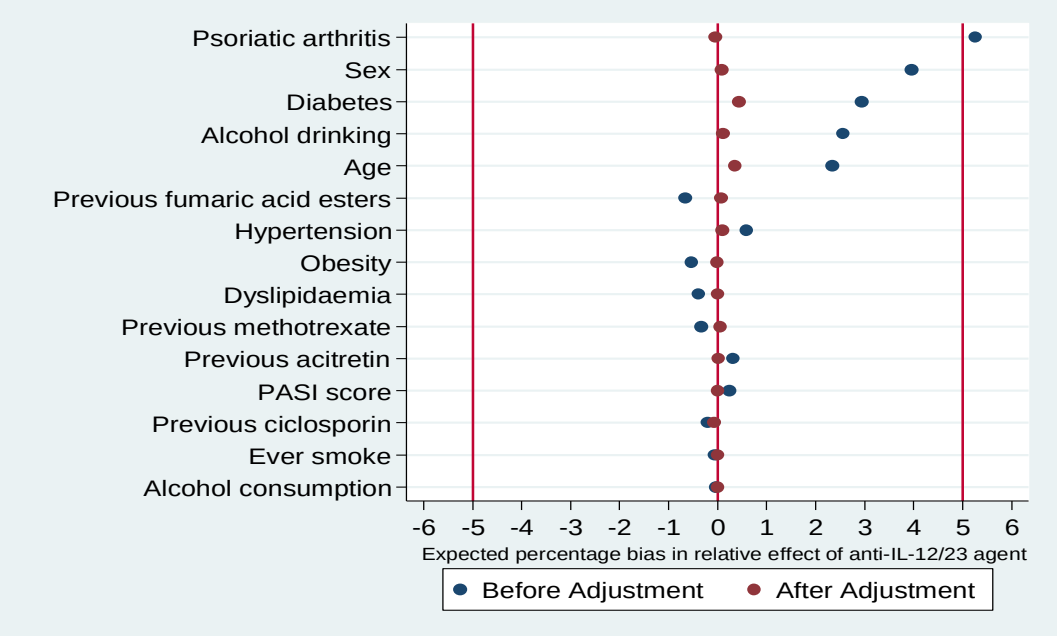
Abbreviations: CI, 95% confidence interval; HR, hazard ratio

Figure 6.4 Distribution of confounders between anti-interleukin-12/23 agent (ustekinumab) and tumour necrosis factor-alpha inhibitors (referent) patients before creating propensity score and after overlap weighting by propensity score for outcomes occurring during drug therapy



Abbreviations: IL, interleukin; PASI, Psoriasis Area Severity Index

Figure 6.5 Distribution of confounders between anti-interleukin-12/23 agent (ustekinumab) and tumour necrosis factor-alpha inhibitors (referent) patients before creating propensity score and after overlap weighting by propensity score for outcomes occurring during drug therapy and extended window period (90 days)



Abbreviations: IL, interleukin; PASI, Psoriasis Area Severity Index

Secondary analyses

A total of 7,657 patients were included in the secondary analyses (ustekinumab, 951; etanercept, 1,313; methotrexate, 2,189 and: adalimumab, 3,204). The proportions of patients with psoriatic arthritis in the ustekinumab (14.1%) and methotrexate (8.9%) groups were lower than in the adalimumab (23.3%) or etanercept (21.9%) groups, as shown in Table 6.5. The ustekinumab, etanercept and adalimumab cohorts had longer durations of follow-up than the methotrexate group (Table 6.6).

Table 6.5 Baseline characteristics of patients receiving ustekinumab, etanercept, methotrexate and adalimumab

Characteristics	Ustekinumab	Etanercept	Methotrexate	Adalimumab
Number of patients (N=7,657)	951	1,313	2,189	3,204
Age (years) (N=7,657)	45 (35 - 54) (n=951)	45 (36 - 53) (n=1,313)	43 (33 - 53) (n=2,189)	44 (35 - 53) (n=3,204)
Sex, male (N=7,657)	590 (62.0) (n=951)	758 (57.7) (n=1,313)	1,127 (51.5) (n=2,189)	1,887 (58.9) (n=3,204)
Ethnicity, white (N=7,647)	853 (89.7) (n=951)	1,209 (92.3) (n=1,310)	1,970 (90.1) (n=2,186)	2,948 (92.1) (n=3,200)
BMI (kg/m^2) (N=6,964)	30.3 (26.2 – 35.7) (n=851)	29.2 (25.8 –34.1) (n=1,193)	28.7 (25.2 – 33.2) (n=1,981)	29.4 (26.0 – 33.7) (n=2,939)
Obese (BMI≥30kg/m^2) (N=6,964)	441 (51.8) (n=851)	546 (45.8) (n=1,193)	824 (41.6) (n=1,981)	1,376 (46.8) (n=2,939)
Ever smoke (yes/no) (N=6,873)	599 (66.6) (n=899)	656 (61.8) (n=1,061)	1,345 (67.7) (n=1,988)	1,885 (64.4) (n=2,925)
Disease duration (years) (N=7,593)	19 (11 - 30) (n=943)	20 (12 - 30) (n=1,307)	17 (8 - 27) (n=2,176)	20 (12 - 29) (n=3,167)
PASI score (N= 6,384)	14.6 (11.2 – 19.2) (n=845)	13.8 (10.8 – 18.6) (n=1,103)	13 (10.3 – 17.8) (n=1,551)	14.2 (11 – 19.5) (n=2,885)
DLQI (N=4,516)	18 (12 - 24) (n=460)	18 (12 - 23) (n=719	15 (11 - 21) (n=1,567)	19 (13 - 24) (n= 1,770)
Comorbidities (N=7,657)				
No comorbidities	315 (33.1)	367 (28.0)	844 (38.6)	989 (30.9)
Psoriatic arthritis	134 (14.1)	288 (21.9)	194 (8.9)	747 (23.3)
Hypertension	241 (25.3)	360 (27.4)	380 (17.4)	743 (23.2)
Diabetes mellitus	98 (10.3)	114 (8.7)	140 (6.4)	243 (7.6)
Dyslipidaemia	98 (10.3)	126 (9.6)	170 (7.8)	309 (9.6)
Other comorbidities	513 (53.9)	693 (52.8)	1,106 (50.5)	1,737 (54.2)
Current alcohol drinking	593 (65.7)	749 (70.5)	1,272 (64.2)	2,105 (71.8)

Characteristics	Ustekinumab	Etanercept	Methotrexate	Adalimumab
(N=6,881)	(n=903)	(n=1,062)	(n=1,982)	(n=2,934)
Alcohol units per week	8 (3 - 15)	10 (4 - 18)	6 (2 - 12)	8 (3 - 15)
in patients consuming	(n=584)	(n=720)	(n=1,246)	(n=2,078)
alcohol (N=4,628)				
Previous treatment of conventional systemic therapies				
Methotrexate	667 (70.1)	865 (65.9)	250 (11.4)	2,259 (70.5)
Ciclosporin	540 (56.8)	684 (52.1)	497 (22.7)	1,901 (59.3)
Acitretin	399 (42.0)	593 (45.2)	610 (27.9)	1,415 (44.2)
Fumaric acid esters	165 (17.4)	331 (25.2)	132 (6.0)	548 (17.1)
Concomitant therapies during drug therapy				
Ciclosporin	71 (7.5)	125 (9.5)	266 (12.2)	330 (10.3)
Acitretin	28 (2.9)	59 (4.5)	91 (4.2)	104 (3.3)
Fumaric acid esters	13 (1.4)	33 (2.5)	31 (1.4)	46 (1.5)
Concomitant therapies during drug therapy or window period (90 days)				
Ciclosporin	74 (7.8)	132 (10.1)	409 (18.7)	359 (11.2)
Acitretin	29 (3.0)	66 (5.0)	185 (8.5)	113 (3.5)
Fumaric acid esters	13 (1.4)	36 (2.7)	93 (4.3)	51 (1.6)

Data are n (%) or median (25th percentile - 75th percentile)

Abbreviations: BMI, body mass index; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area Severity Index

During drug therapy, major CVEs occurred in 7, 5, 7 and 19 patients receiving ustekinumab, etanercept, methotrexate and adalimumab, respectively; during the extended exposure window period, major CVEs occurred in 7, 6, 9 and 23 patients, respectively. The incidence rates associated with exposure to ustekinumab was numerically higher than those associated with adalimumab and methotrexate but these differences were not significant. The median times to onset of major CVEs in all groups and analyses were about 1 year but etanercept had the longest onset of major CVEs compared to the other groups (Table 6.6).

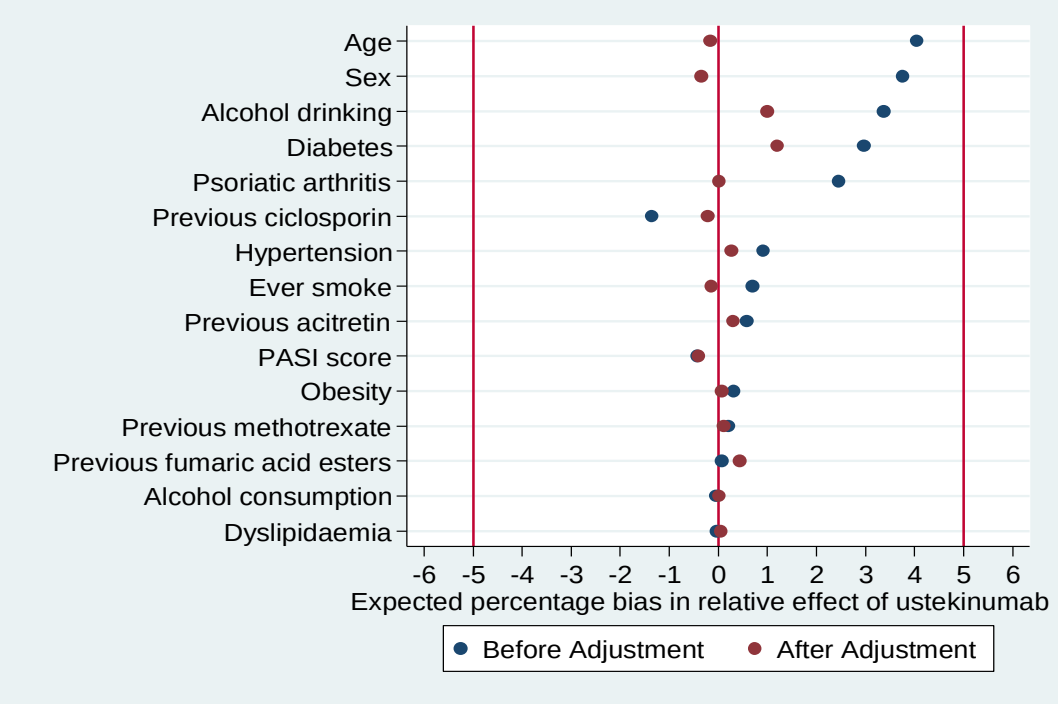
Table 6.6 Incidence rates and incidence rate ratios among patients receiving ustekinumab, etanercept, methotrexate and adalimumab

	Ustekinumab	Etanercept	methotrexate	Adalimumab
Outcome during drug therapy				
Total patient-years	1,936.56	2,905.99	3,650.81	6,851.23
Patient-years of follow-up (median, p25-p75)	1.76 (0.92 – 2.96)	1.67 (0.69 – 3.20)	1.18 (0.59 – 2.29)	1.69 (0.84 – 3.07)
Number of major cardiovascular events	7	5	7	19
Incidence rate per 1,000 patient-years (95% CI)	3.61 (1.72 – 7.58)	1.72 (0.72 – 4.13)	1.92 (0.91 – 4.02)	2.77 (1.77 – 4.35)
Incidence rate ratio	1.30 (0.46 - 3.24)	0.62 (0.18 – 1.72)	0.69 (0.25 - 1.72)	Reference
Incidence rate ratio	1.89 (0.56 - 6.30)	0.90 (0.22 - 3.28)	Reference	1.45 (0.58 - 4.07)
Duration between the start of exposure to development of the outcome (years) (median, p25-p75) (only patients experiencing the outcome)	1.06 (0.59 – 1.94)	1.29 (1.08 – 1.82)	0.99 (0.86 – 1.60)	0.90 (0.46 – 2.29)
Outcome during drug therapy or window period (90 days)				
Total patient-years	2,167.61	3,226.03	4,185.94	7,632.87
Patient-years of follow-up (median, p25-p75)	2.01 (1.16 – 3.21)	1.92 (0.93 – 3.45)	1.43 (0.84 – 2.53)	1.94 (1.09 – 3.32)
Number of major cardiovascular events	7	6	9	23
Incidence rate per 1,000 patient-years (95% CI)	3.23 (1.54 – 6.77)	1.86 (0.84 – 4.14)	2.15 (1.12 – 4.13)	3.01 (2.00 – 4.53)
Incidence rate ratio	1.07 (0.39 – 2.58)	0.62 (0.21 – 1.56)	0.71 (0.29 – 1.60)	Reference
Incidence rate ratio	1.50 (0.48 – 4.53)	0.87 (0.25 – 2.72)	Reference	1.40 (0.62 – 3.44)
Duration between the start of exposure to development of the outcome (years) (median, p25-p75) (only patients experiencing the outcome)	1.06 (0.59 – 1.94)	1.19 (1.06 – 1.82)	0.99 (0.86 – 1.60)	0.90 (0.44 – 2.29)

Abbreviations: 95% CI, 95% confidence interval; p25 - p75, 25th percentile - 75th percentile

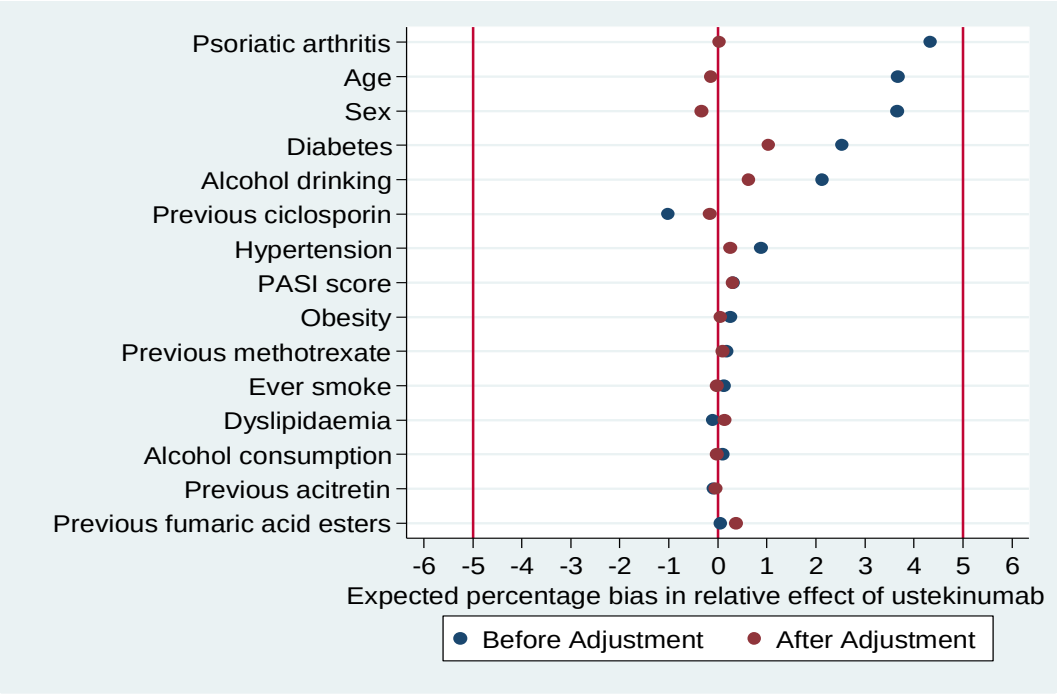
The proportionality test for all comparisons and both analysis times showed no violation of proportional hazard assumptions. Moreover, the expected percentage bias achieved a good balance in all analyses, after adjusted for overlap weights by propensity score (Figure 6.6 – 6.11).

Figure 6.6 Distribution of confounders between ustekinumab and adalimumab (referent) patients before creating propensity score and after overlap weighting by propensity score for outcomes occurring during drug therapy



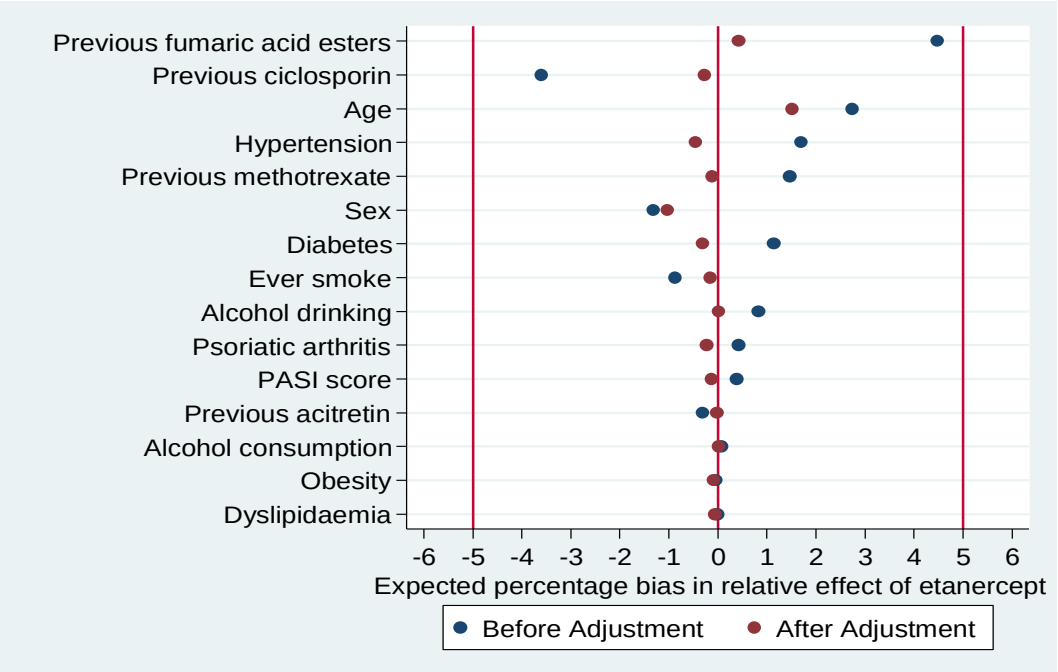
Abbreviation: PASI, Psoriasis Area Severity Index

Figure 6.7 Distribution of confounders between ustekinumab and adalimumab (referent) patients before creating propensity score and after overlap weighting by propensity score for outcomes occurring during drug therapy and extended window period (90 days)



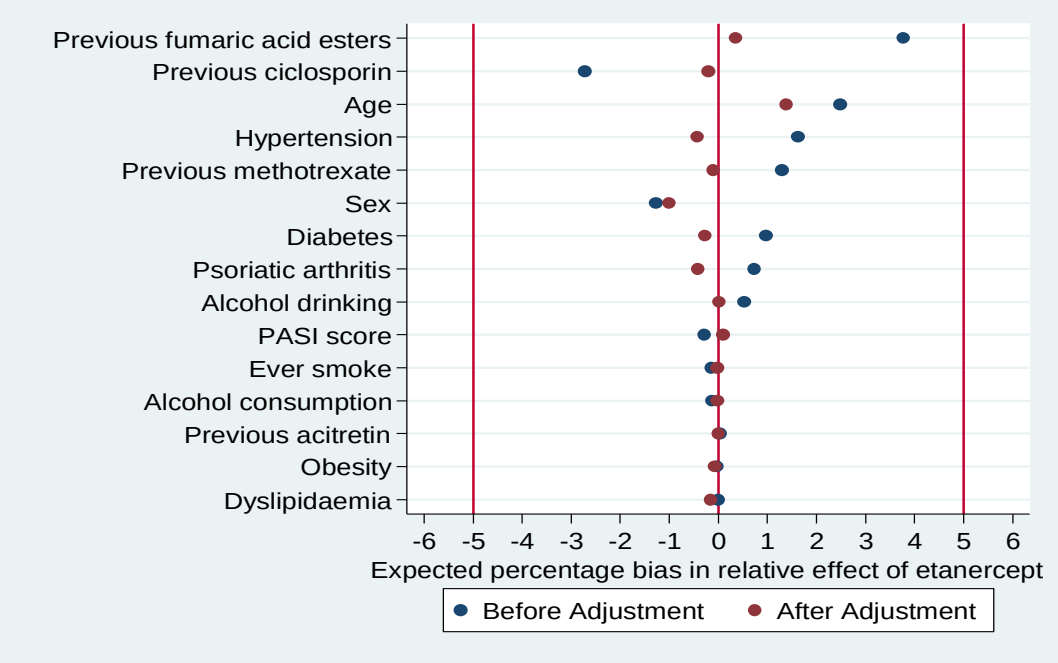
Abbreviation: PASI, Psoriasis Area Severity Index

Figure 6.8 Distribution of confounders between etanercept and adalimumab (referent) patients before creating propensity score and after overlap weighting by propensity score for outcomes occurring during drug therapy



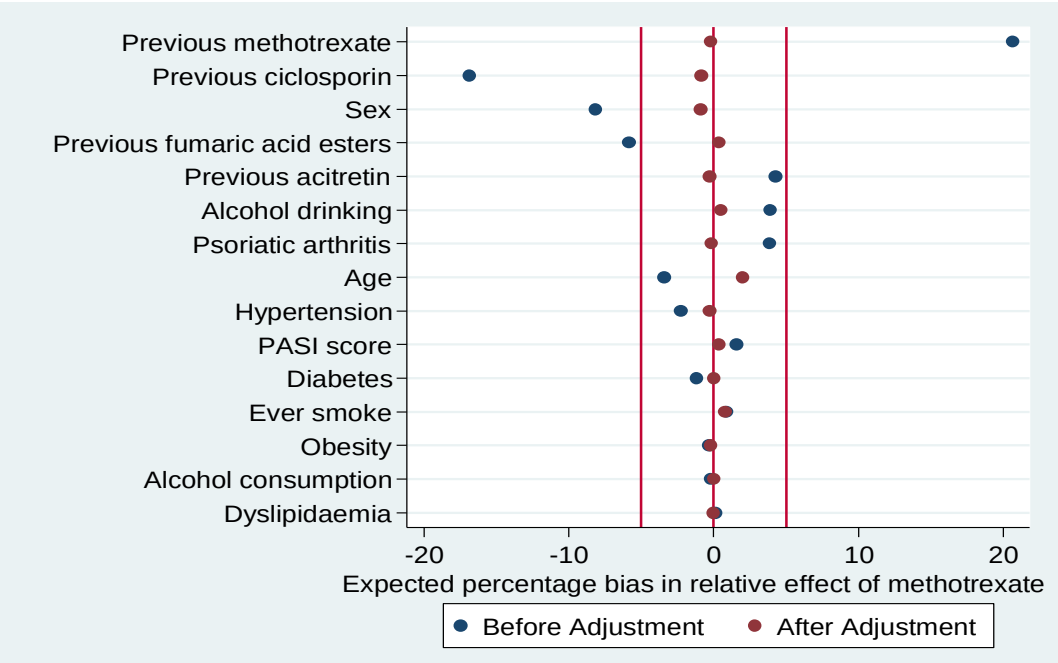
Abbreviation: PASI, Psoriasis Area Severity Index

Figure 6.9 Distribution of confounders between etanercept and adalimumab (referent) patients before creating propensity score and after overlap weighting by propensity score for outcomes occurring during drug therapy and extended window period (90 days)



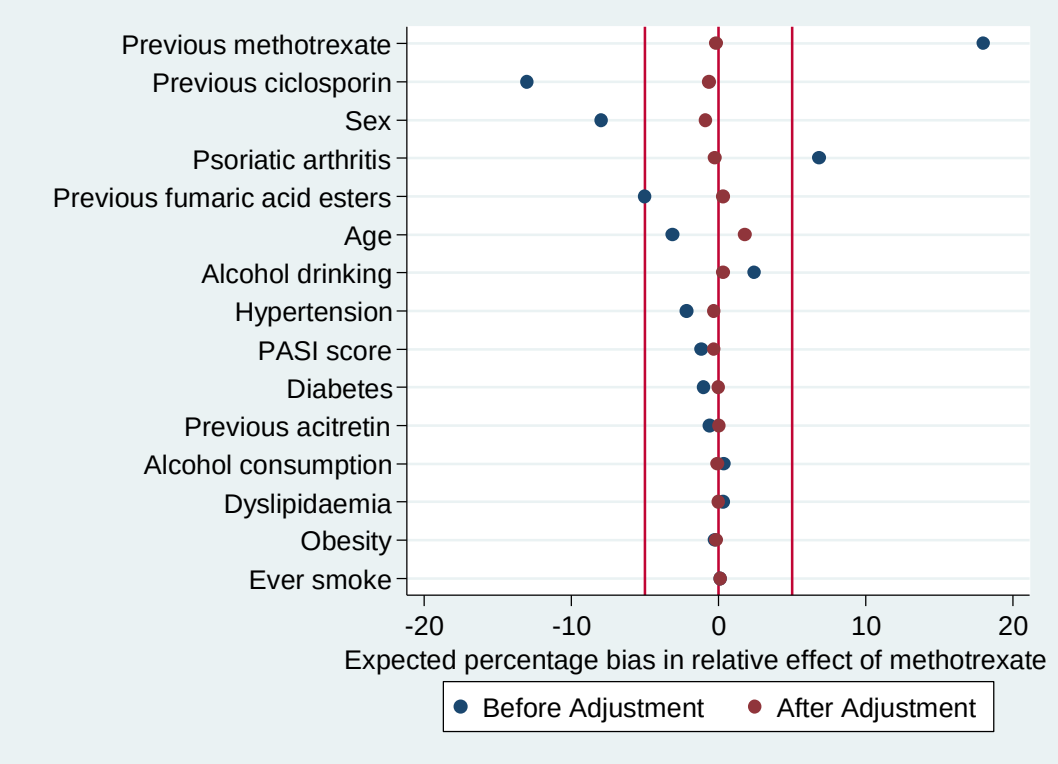
Abbreviation: PASI, Psoriasis Area Severity Index

Figure 6.10 Distribution of confounders between methotrexate and adalimumab (referent) patients before creating propensity score and after overlap weighting by propensity score for outcomes occurring during drug therapy



Abbreviation: PASI, Psoriasis Area Severity Index

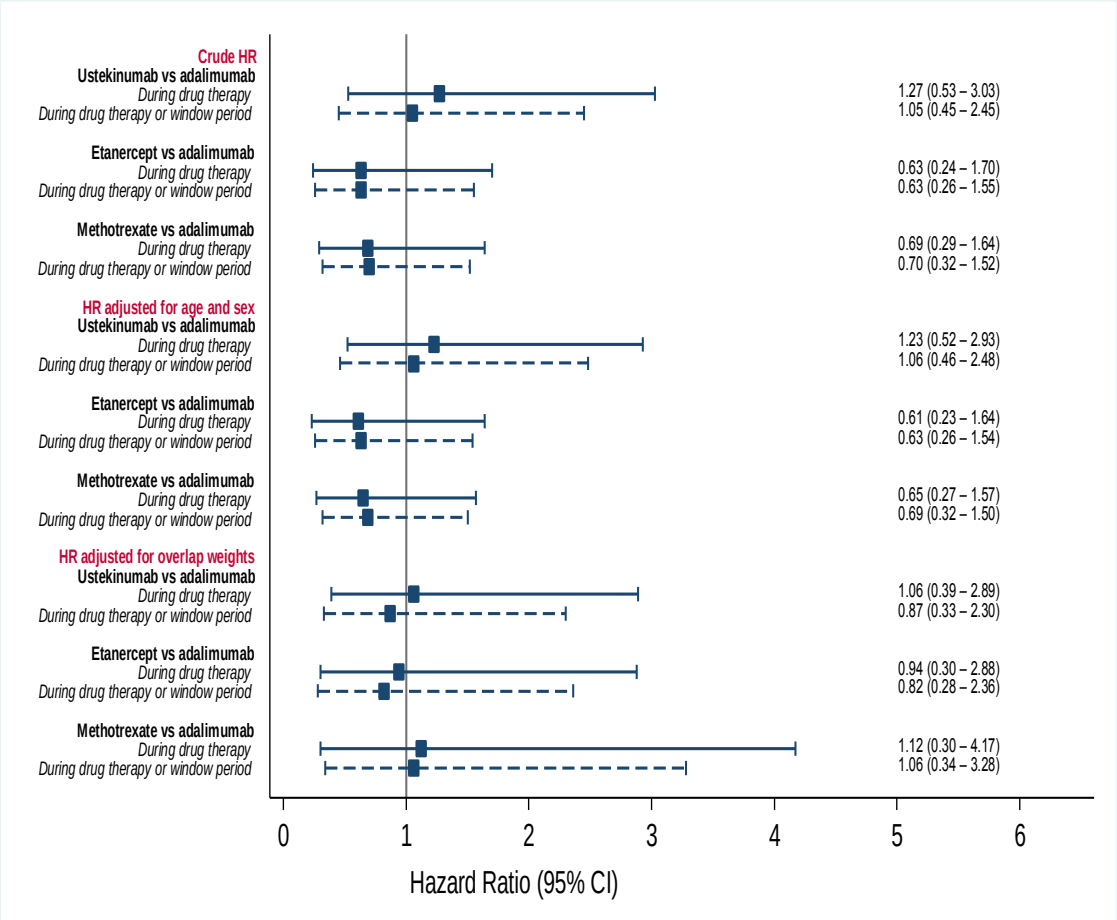
Figure 6.11 Distribution of confounders between methotrexate and adalimumab (referent) patients before creating propensity score and after overlap weighting by propensity score for outcomes occurring during drug therapy and extended window period (90 days)



Abbreviation: PASI, Psoriasis Area Severity Index

There were no significant differences in the risk for major CVE occurring during drug therapy or the extended exposure window period when patients using ustekinumab, etanercept or methotrexate were compared with those using adalimumab as shown in (Figure 6.12).

Figure 6.12 Crude and adjusted hazard ratios (95% confidence interval) for major cardiovascular events associated with different psoriasis therapies for comparisons of ustekinumab, etanercept or methotrexate with adalimumab (referent group)



Abbreviations: CI, confidence interval; HR, hazard ratio

6.5 Discussion

In this large prospective cohort study, the results showed no significant differences in the risk of major CVEs between biologic therapies in adult patients with chronic plaque psoriasis. Moreover, the risk of major CVEs for methotrexate was not significantly different from adalimumab. These findings are derived from propensity score-adjusted models taking into account a range of important cardiovascular risk factors. These findings were consistent for separate analyses comparing the risk of major CVEs both during therapy and for an extended exposure window period. These results indicate that the risk of major CVEs should not a major discriminator for choosing biologic therapies for managing psoriasis.

Earlier observational studies had a number of differences which make comparison with this study difficult: notably, different comparators, definitions of cardiovascular outcomes, types of databases and healthcare systems, an involvement of pharmaceutical companies marketing biologic therapies for the treatment of psoriasis, including participants with prior CVEs in the

studies, and not controlling for some important cardiovascular risk factors.[7–11] The results of these previous studies suggested benefits of biologic therapies in relation to risk of cardiovascular outcomes. One study suggested that TNFi-treated patients (adalimumab, etanercept and infliximab; n=9,148) had a significantly lower risk of composite and individual CVEs (MI; stroke or transient ischemic attack; or unstable angina) when compared with those treated with methotrexate (n=8,581).[7] In addition, two cohort studies suggested that TNFi (n1=1,463 and n2=11,410) significantly decreased the risk of MACEs when compared with topical therapies (n=13,112) and the risk of major CVEs (MI; stroke or transient ischemic attack; or unstable angina) when compared with phototherapy (n=12,433).[10,11]

These three studies were conducted using US claims databases. Patients' characteristics in these databases might be different from those in the current study since the US has a different healthcare system from the UK. The UK has universal healthcare coverage. This allows all UK residents to access healthcare service. Moreover, healthcare professionals tend to provide the services according to the national guidelines such as the NICE and SIGN guidelines. These guidelines recommend using biologic therapies (the most effective treatments) as the last choice for the treatment of psoriasis in patients with moderate-severe psoriasis.[45,51] Thus, patients tended to have a similar severity of psoriasis in the current study.

The US does not have universal healthcare coverage like the UK. Thus, data of some patients with psoriasis might not exist in these databases. In addition, healthcare professionals do not have to follow psoriasis treatment guidelines in the US. Therefore, these studies might have a problem with mixing patients with different levels of psoriasis severity. The severity of psoriasis among patients receiving biologic therapies in these databases might be different or have less severity than that among patients in the BADBIR. Since the severity of psoriasis can influence the development of CVEs, this factor could bias the results of the studies. As these databases are primarily collected for financial purpose, if prescriptions are filled outside of the insurance plan, it may be absent from the claims data.[411] This might also cause misclassification bias for these studies.

Moreover, all of these studies were supported by pharmaceutical companies marketing biologic therapies for the treatment of psoriasis. These pharmaceutical companies involved in study design, interpretation of data, review or/and approval of the publications in two out of these three studies.[10,11] The results of these studies might be susceptible to bias while the current study was free from pharmaceutical influence. No researchers from pharmaceutical companies involved in the current study. These factors might be reasons why their results were different from the results of the study in this thesis.

A further study using a Danish nationwide cohort defined CVEs as composite MI, stroke and cardiovascular death. It found a significantly lower risk of CVEs in TNFi (n=959) and methotrexate (n=3,564) treated groups while the risk in those treated with ustekinumab (n=178) was similar to those using other therapies (topical, phototherapy and climate therapy;

n=3,961).[9] Since the sample size of the ustekinumab group was very small in the earlier study, it is unlikely that any difference in the risk of CVEs would be detected for this comparison. Since the reference therapies in all of these earlier studies are offered before biologic therapies for the treatment of psoriasis[45,51], patients in the reference groups were likely to have less severe psoriasis. The risk of CVEs can be influenced by the severity of psoriasis.[220] Thus, this factor might be one of the reasons why most of their results were different from the results in this thesis. In line with these findings, an earlier cohort study found that patients treated with biologic therapies (including ustekinumab, adalimumab, etanercept, alefacept and efalizumab) (n=7,682 at enrolment) had a similar risk of CVEs (nonfatal-MI, nonfatal-stroke and CV death) when compared to those treated with non-biologic agents (n=5,576 at enrolment).[8] Of related interest, two RCTs examining the impact of adalimumab (TNFi) on aortic vascular inflammation in patients with moderate-severe psoriasis also recently reported that adalimumab did not improve aortic vascular inflammation after 52 weeks of treatment.[328,412]

Chapter 7

Discussion

7.1 Discussion

The overarching aims of this PhD thesis were: firstly to compare the prevalence of comorbidities in patients with psoriasis against participants without psoriasis (the results of this assessment are presented in Chapter 4); and secondly, to examine the impact of biologic therapies on the risk of CVEs in patients with plaque psoriasis. The detailed results related to this are described in Chapters 5 and 6. The aim of this Discussion chapter is to summarise the key findings from my PhD and discuss their contribution to current knowledge. The strengths and limitations of the work are also discussed. In addition, the clinical implications from the findings and the proposals for future research building from this research programme are also presented in this chapter.

7.1.1 Psoriasis and comorbidities

Patients with psoriasis are at high risk of a number of comorbidities. However, previous studies reporting their prevalence rates and associations had wide ranges. Furthermore, many earlier studies examined the prevalence of specific comorbidities in patients with psoriasis but very few studies reported on both the burden of physical and mental health comorbidities. Population-based cross-sectional studies using databases designed for preventing and improving diagnosis of disease are scarce. Generally, these studies used electronic healthcare records for their investigation. The results from the cross-sectional study (Chapter 4) estimated the prevalence rates of physical and mental health comorbidities in patients with and without psoriasis. The UK Biobank database which broadly represents the middle-to-old aged UK population was used for this study. The UK Biobank was designed to support a diverse range of research to prevent and improve diagnosis of disease.[353] The findings suggested that psoriasis was associated with an increased prevalence of a number of physical and mental comorbidities. Moreover, patients with psoriasis had higher prevalence rates for a number of established cardiovascular risk factors including hypertension, high cholesterol, diabetes, obesity, smoking and inflammatory arthritis than participants without psoriasis. These findings relating to the higher burden of cardiovascular risk factors were consistent with those in previous studies.[115,185]

Chapter 4 also found that patients with psoriasis had an elevated risk of a history of MI and peripheral vascular disease, which has also been reported in some earlier studies.[141,220] Shared inflammatory pathways between psoriasis and atherosclerosis; and the expression of proinflammatory cytokines might lead to the development of these CVEs.[197,360] However, a higher prevalence of previous stroke or transient ischemic attack was not apparent in this study. This was consistent with UK and Taiwanese cross-sectional studies.[124,141] In addition, this study found that heart failure/pulmonary oedema, atrial fibrillation and a history of venous thromboembolic disease were not significantly associated with psoriasis.

Psoriatic arthritis is one of the most common comorbidities in psoriasis patients. As rheumatoid arthritis is a common misdiagnosis of psoriasis arthritis[81], both terms were grouped as inflammatory arthritis in this study. The results showed the largest difference in prevalence rates

between patients with and without psoriasis [16.9% vs 1.1%, adjusted PR 15.10 (95% CI 14.22 – 16.05)]. Moreover, osteoarthritis and gout which are also common misdiagnoses of psoriatic arthritis[358,359] showed the higher prevalence rates and the increased PRs in patients with psoriasis.

This study found that psoriasis was associated with inflammatory bowel disease which was also found in previous studies.[91–93,95] Furthermore, a higher prevalence of cirrhosis/liver failure including alcoholic liver disease/alcoholic cirrhosis was observed in patients with psoriasis in this study. Previously, two small-scale Italian studies reported that psoriasis was related to an elevated risk of NAFLD but the prevalence rates in these studies (prevalence rates for NAFLD: 47 - 59.2% in patients with psoriasis and 28% in patients without psoriasis) were much higher than the prevalence rate of cirrhosis/liver failure including alcoholic liver disease/alcoholic cirrhosis presented in Chapter 4 (0.3% in patients with psoriasis and 0.1% in patients without psoriasis).[87,88] The large difference in estimates from these studies might be due to the different definitions of the outcomes and outcome measurements. Chapter 4 mainly focuses on cirrhosis and liver failure which are serious diseases and life-threatening and have not been routinely investigated in previous studies while NAFLD defined by the Italian studies covered a wide range of hepatic conditions. Moreover, the outcome measurements among these studies were also different. The Italian studies used abdominal ultrasound and laboratory tests to define the outcomes while participants in the study in this thesis self-reported their liver diseases at the enrolment to the UK Biobank. The rates reported in Chapter 4 are similar to the prevalence rates of liver disease reported in a UK cross-sectional study comparing patients with psoriasis [1.0% (92/9,035)] and the general population [0.7% (659/90,350)] using the THIN dataset (electronic health records).[141] The increased risk of cirrhosis/liver failure presented in patients with psoriasis might be due to liver dysfunction. An imaging study found that patients with psoriasis had subclinical inflammation in the liver.[360] In addition, significantly increased PRs of renal failure were observed in patients with psoriasis [crude PR: 1.88 (95% CI 1.21 – 2.93) and PR adjusted for age, sex and deprivation: 1.81 (95% CI 1.16 – 2.82)]. Since psoriasis is associated with diabetes, hypertension, microalbuminuria and signs of subclinical glomerular dysfunction[115,413,414], these factors can contribute to an increased prevalence of renal failure. Only a few earlier studies which examined the association between psoriasis and renal failure have also reported on this relationship.[124,141]

Patients with and without psoriasis had similar frequencies of alcohol consumption in this study. Nevertheless, more patients with psoriasis had a history of alcohol dependence (0.4% vs 0.2%). The results of PRs also showed the significantly increased crude PR of 2.47 (95% CI 1.62 – 3.78) and adjusted PR of 2.18 (95% CI 1.43 – 3.33). The results might imply that patients with psoriasis were more likely to drink excessive amounts of alcohol than participants without psoriasis. The alcohol problem among patients with psoriasis was found in a recent UK-based cohort study.[361] It found that psoriasis patients had about a 60% greater risk of alcohol-related mortality compared with the general population and 85% of psoriasis patients with alcohol-related deaths had a history of hospital admission due to a chronic alcohol-related condition.

Moreover, Chapter 4 shows higher prevalence rates of chronic sinusitis, irritable bowel syndrome, diverticular disease/diverticulitis or migraine which has not been reported in previous studies.

Importantly, the study also found that patients with psoriasis had elevated prevalence rates for mental health comorbidities which could lead to decreased quality of life. These findings were consistent with previous evidence.[61,62] Recently, a large population-based cohort study reported a higher prevalence of mental illness and modest increase in the risk of self-harm, but found overall a lower risk of suicide in patients with psoriasis.[362] It is possible that this lower risk could be accounted for by closer monitoring for physical and mental illness by clinicians given the more frequent healthcare contact of patients with psoriasis than the general population or competing risk due to other causes of death.[362]

Importantly, this large cross-sectional study found that patients with psoriasis experienced far more overall comorbidities compared to those without psoriasis; this was apparent for both physical and mental health comorbidities. There were significant trends towards ORs with the increasing numbers of comorbidities. Moreover, some comorbidities can lead to the development of other diseases. For example, psoriasis patients with diabetes might later develop CVD. These factors might increase the number of comorbidities in patients with psoriasis.

The study evaluating comorbidities among patients with and without psoriasis had both strengths and potential limitations that should be considered in interpreting the findings presented. The UK Biobank, a large prospective cohort study, is an important resource for examining patients' characteristics, the prevalence rates and the associations of comorbidities in patients with and without psoriasis. It has recruited over 500,000 middle-to-old aged participants. Middle and old aged people have an increased likelihood of developing serious diseases. The UK Biobank was designed for capturing clinical information, comorbidities and participants' lifestyle characteristics. This prospective cohort study has a number of advantages in comparison to analyses undertaken using electronic health records may have particular problems with inaccuracy or incompleteness of recording.[415] For example, the extent of missing data for smoking status in the UK Biobank was much lower than that which has been reported using the CPRD (0.6% vs 11.11%).[216] Moreover, lifestyle habits (e.g. physical activity) which can have an influence on the development of comorbidities are not routinely captured in electronic healthcare records.

To my knowledge, this is the first cross-sectional study of the UK Biobank assessing the prevalence of comorbidities in patients with psoriasis. Owing to the large size of the UK Biobank database and detailed data collection, it had the potential to examine a range from low – high prevalence of comorbidities. Since participants with and without psoriasis came from the same database, assessment centres, and same time-window; these might be able to minimise selection bias, information bias and detection bias. It is important to consider though whether

patients with a skin disease are more likely to have other conditions diagnosed whilst visiting their clinicians for their skin condition.[343] If this was the case then it could potentially result in greater detection of comorbidities among psoriasis patients recorded in the health records than the non-psoriasis participants in the UK Biobank.

This study used a self-report method to identify comorbidities. Although the use of self-reported comorbidities has a limitation due to the potential for recall bias, there is no clear reason to believe that recall would differ between those with psoriasis or not. The UK Biobank nurses are trained to capture relevant data on comorbidities and thus likely to minimise the risk of recall or misclassification bias. This method of data collection has been used in many other studies and found to be a suitable method to capture comorbidities.[416]

However, this study still had some limitations. Diagnoses of diseases were not subsequently confirmed by clinicians. This could affect the true prevalence rates of psoriasis and comorbidities. Since most participants in the UK Biobank are white, it may limit the generalisability of the results to other ethnic groups. As participants had to respond to the invitation letter from the UK Biobank, this study might have a healthy volunteer selection bias. The volunteering participants might have different characteristics from the general population.[417] A published UK Biobank study found that the participants in this database were more likely to be female and live in less socioeconomically deprived areas compared with non-participants.[354] These potential limitations should be considered when interpreting the findings.

7.1.2 Biologic therapies and risk of major cardiovascular events

The question of whether biologic therapies influence the risk of major CVEs in patients with psoriasis is of concern to healthcare professionals, researchers, patients and policy makers. The results of Chapters 5 and 6 showed that biologic therapies were not significantly associated with the risk of MACEs when compared with placebo or the different doses of the same biologic therapy; and the risk of major CVEs when compared with different biologic therapies or methotrexate.

Chapter 5 presents the results of the systematic review and meta-analysis of RCTs. It included RCTs reporting AEs in adult patients with plaque psoriasis who received any licensed biologic therapies for the treatment of psoriasis approved up until 31st March 2016. This study involved TNFi (adalimumab, etanercept and infliximab), anti-IL-12/23 agent (ustekinumab) and anti-IL-17A agents (secukinumab and ixekizumab). It found that there was no significant difference in the risk of MACEs associated with the use of overall biologic therapies; TNFi; anti-IL-12/23 agent or anti-IL-17A agents when compared with placebo among adults with plaque psoriasis. In addition, no difference in the risk was observed for the comparisons of the different licensed doses of ustekinumab (45 mg vs 90 mg) or secukinumab (150 mg vs 300 mg) during the relatively short-term follow-up of treatment during trials.

This study is the largest systematic review and meta-analysis examining the association between currently licensed doses of biologic therapies and MACEs in adults with plaque psoriasis conducted to date. The findings extend the result of an earlier meta-analysis published in 2011.[336] The previous meta-analysis included a currently unlicensed biologic therapy (briakinumab) for the treatment of psoriasis and examined the risk using absolute risk difference which is a less appropriate method than Peto OR for detecting rare events (lower than 1%).[366] However, the findings for anti-IL-12/23 agent (ustekinumab) in this study presented in this thesis contrasted to that in the another meta-analysis published in 2013.[337] It found that anti-IL-12/23 agents (ustekinumab and briakinumab) significantly increased the risk of MACEs in adults with psoriasis. These different results might be due to the inclusion of the unlicensed biologic briakinumab in the meta-analysis. This biologic therapy was discontinued during the development programme due to concern regarding whether anti-IL-12/23 agents could be associated with an increased risk of CVD.[333,335,350] One important limitation of the interpretation of these earlier meta-analyses was that they included patients treated with both non-licensed and licensed doses of biologic therapies whilst the meta-analysis presented in this thesis focussed only on those patients receiving biologic therapies at licensed dose regimens. In addition, Chapter 5 includes the new biologic therapies that had not been investigated in earlier meta-analyses. Specifically, the anti-IL-17A agents (secukinumab and ixekizumab) were compared with placebo and between different licensed doses of ustekinumab (45 mg vs 90 mg) and secukinumab (150 mg vs 300 mg). However, the numbers of included patients for these comparisons were relatively small (4,034 patients for the comparison of anti-IL-17A agents and placebo; 2,012 patients for the comparison of the different doses of ustekinumab; and 2,347 patients for the comparison of the different doses of secukinumab).

The work presented in Chapter 5 has several strengths. A systematic review and meta-analysis, the top hierarchy of evidence-based practice, was used to examine the impact of biologic therapies on the risk of MACEs in adults with plaque psoriasis. This study involved 12,596 psoriasis patients treated with biologic therapies. It considered all licensed doses of biologic therapies for the treatment of psoriasis and far more extensive searches for eligible trials were conducted in comparison with the previous meta-analyses.[336,337] The sources included published and unpublished documents from the regulatory websites, pharmaceutical websites and trial registries to ensure the optimal detection of eligible trials. Moreover, a range of comparisons was considered; both biologic therapies vs placebo and the different doses of the same biologic therapies. Furthermore, both Peto ORs and Mantel-Haenszel risk differences were calculated to ensure that different methods of assessment did not change the results.

Nonetheless, several important limitations should be considered when interpreting the findings of the meta-analysis presented in this thesis. Firstly, the primary aim of all the included trials was to examine the efficacy of the treatments and only 10 trials explicitly provided a definition of MACEs and established a committee for adjudicating suspected cases. Most of the included trials had a relatively small sample size and a short duration of the randomised controlled phase of treatment (ranging from 10 to 30 weeks). These factors would impact on the power of the

included studies to detect a change in the risk of MACEs and this uncertainty was reflected by the wide CIs surrounding some of these risk estimates. For instance, ustekinumab has been suggested to increase this risk during the initial stage of therapy because of temporary increases in inflammatory mediators.[418] A phase 2 study showed that serum levels of IL-12/23p40, which is pro-atherogenic, in patients receiving ustekinumab dramatically increased at week 12 and decreased to little above baseline levels by week 32.[419] Thus, the assessment of the potential association requires continued surveillance of emerging trial data. In cardiovascular research, it is also well established to use composite outcomes including MACEs to detect rare events; this will increase the power to detect clinically important differences in event rates.[420] Ideally, the recent calls to facilitate the sharing of clinical trial data will also provide new opportunities to examine individual patient level data from RCTs thereby enabling more robust time-to-event meta-analysis to be performed.[421]

The majority of the included studies were phase 3 trials which tend to enrol patients with fewer comorbidities than those seen in routine clinical practice and also exclude elderly patients who are at increased risk of MACEs. Thus, the background risk for both the exposed and non-exposed groups is likely to be lower which may limit the generalisability of the findings.

The existing RCTs and the earlier cohorts evaluating the association between major CVEs and biologic therapies for the treatment of psoriasis had some limitations. Therefore, it requires well-designed cohort studies to examine this association. Chapter 4 showed that patients with psoriasis had a higher risk of cardiovascular risk factors such as psoriatic arthritis, diabetes, hypertension, dyslipidaemia, smoking and obesity. These factors should be taken into account when examining the impact of biologic therapies on the risk of major CVEs in adults with psoriasis.

Chapter 6 presented the results of the prospective cohort study which examined the risk of major CVEs related to biologic therapies in patients with plaque psoriasis using the BADBIR dataset. There was no significant difference in the risk of major CVEs between biologic therapies in adult patients with moderate-severe plaque psoriasis when taking into account a range of important cardiovascular risk factors. In addition, a significant difference in the risk was not observed in the comparison of adalimumab and methotrexate. The results were consistent for separate analyses comparing the risk of major CVEs both during drug therapy and for an extended exposure window period.

Earlier cohort studies suggested impressive benefits of biologic therapies for the treatment of psoriasis in relation to risk of cardiovascular outcomes.[7–11] However, the study designs of these studies had many limitations. Specifically, they used inappropriate comparators, included participants with prior CVEs, and did not control for some important cardiovascular risk factors.[7–11] These factors could bias the results of the assessment. None of the earlier cohort studies has compared the risk of cardiovascular outcomes between biologic therapies. Biologic therapies in these studies were compared with other psoriasis therapies (e.g. topical therapies)

which tend to be used in patients with less severity of psoriasis. It has previously been suggested that patients with severe psoriasis have a higher risk of CVEs.[220] To examine the impact of biologic therapies, participants in comparison groups should have a similar severity of disease. Furthermore, psoriasis patients with prior CVEs have a high likelihood of recurrent CVEs compared with psoriasis patients without a history of major CVEs. All of these limitations in study designs could impact on the potential for bias in the assessment of any risk. These are likely to be the main reasons why the findings from the earlier cohort studies contrasted to those of the prospective cohort study in this thesis which showed no significant difference in the risk of major CVEs for all comparisons.

This study has several important strengths. To my knowledge, this is the first large prospective cohort study to compare the risk of major CVEs between different biologic therapies in adult patients with plaque psoriasis. The risk of bias was reduced by using a new-user study design for the biologic cohorts[422], and a propensity score technique for examining the impact of biologic therapies on the risk of major CVEs. The propensity score technique adequately controlled for measured cardiovascular confounders between comparison groups and these methods have not been used in the earlier cohort studies examining cardiovascular risk. Secondly, patients who had experienced prior major CVEs were excluded so as to minimise bias.

However, some study limitations still existed. First, although measured confounders including the most important cardiovascular risk factors were controlled for, the effects of residual confounding due to other unmeasured variables such as physical activity and dietary factors cannot be excluded. Second, some aspects of cardiovascular risk factor management may be specific to this national cohort and therefore the results may not be generalisable to patients managed in different healthcare systems. Third, the small numbers of major CVEs and participants and limited follow-up may have an impact on the power for these analyses. Moreover, the impact of biologic therapies on the risk of major CVEs may change over the long-term. Therefore, there is a need for continued surveillance. The BADBIR can be used to explore this association as it continues to collect safety information in psoriasis patients receiving biologic therapies over the longer-term.

Chapter 5 found that the overall rate for MACEs associated with TNFi (adalimumab, etanercept and infliximab) was 0.05% in adult patients with plaque psoriasis. This rate was based on the existing RCTs while the prospective cohort study of this thesis using the BADBIR dataset showed the higher rates of major CVEs for TNFi (etanercept and adalimumab). The rates were 0.53% for the events occurring during drug therapy and 0.64% for the events during the extended exposure window period. Even if both studies included different TNFi and defined the cardiovascular outcomes slightly differently, it can be seen that this prospective cohort was able to capture cardiovascular outcomes. Therefore, prospective cohort studies with robust study designs are essential to continue to evaluate the long-term safety profile of biologic therapies for the treatment of psoriasis.

7.2 Implications for clinical practice and policy

The findings in this thesis will be of interest to healthcare professionals, patients and policy makers. It provides a clearer picture of the magnitude and association of physical and mental health comorbidities in patients with psoriasis and the cardiovascular safety profile of biologic therapies used for treatment of the disease.

Patients with psoriasis were more likely to have deleterious lifestyle habits (e.g. smoking and no physical activity) and a number of physical and mental health comorbidities including cardiovascular risk factors. Some of these conditions can lead to other serious conditions or consequences. For example, psoriasis patients with diabetes and hypertension may later develop CVEs. The mental health comorbidities which were prevalent in patients with psoriasis are likely to reflect the psychosocial impact and lead to a negative impact on quality of life.[61] Therefore, regular lifestyle modification (e.g. smoking cessation), screening and monitoring of physical and mental health comorbidities may reduce the likelihood of developing new comorbidities and/or serious consequences as well as mitigating their severity. Earlier RCTs have shown that dietary interventions with or without increased physical activity which was used to reduce weight in overweight or obese patients with psoriasis could also reduce the severity of psoriasis and improve quality of life.[423,424] These results support that lifestyle modification plays an important role in the management of psoriasis.

As psoriasis patients had a high likelihood of having many chronic comorbidities, these diseases tend to be managed by polypharmacy and several different clinical specialities. Therefore, the use of multiple concurrent medications may lead to drug interactions, side-effects and lower medication adherence.[425] These problems can be managed by an efficient multidisciplinary team (e.g. clinicians and pharmacists) and an efficient linkage of medication records among general practices, hospitals and pharmacies. These systems may help psoriasis patients gain maximum benefit and less harm from their medicines. In addition, the prevalence of psoriasis has steadily increased owing to an increasing population living longer in the UK.[4] Therefore, this has important implications for healthcare service delivery and resource allocation.

The findings from Chapters 5 and 6 found that there was no significant difference in the risk of major CVEs in psoriasis patients treated with biologic therapies compared with placebo or the different doses of the same biologic therapies. Moreover, no significant difference in the risk of major CVEs was observed in patients receiving biologic therapies compared with different biologic therapies or methotrexate. These findings were based on the RCTs and registry data (BADBIR) which has a greater external validity than the former. Thus, the results of both studies suggested the same conclusion that the risk of MACEs or major CVEs is not a discriminator for choosing biologic therapies for moderate-severe plaque psoriasis in real-life practice. Clinicians should prescribe biologic therapies or methotrexate for patients with plaque psoriasis based on other factors such as efficacy and non-major CVEs side-effects of psoriasis therapies,

concomitant drugs and comorbidities. However, the findings are based on 10 – 30 weeks of drug exposure in RCTs and about 2 years of exposure in the prospective cohort study. Drug regulatory bodies which are responsible for approving medicines and ensuring that the benefits of the medicine outweigh the known risks can use the findings from these studies for their considerations. As patients with psoriasis in real-life practice tend to be different from those in clinical trials, the need for continued post-authorisation surveillance for cardiovascular safety is needed. Thus, they may encourage pharmaceutical companies, healthcare professionals, researchers and patients to continue to monitor the safety of all biologic therapies used for the treatment of psoriasis. This measurement will ultimately improve understanding of the cardiovascular safety profile of these novel agents.

7.3 Recommendations for future research

The UK Biobank study in the thesis suggested that patients with psoriasis were more likely to have a number of comorbidities compared with participants without psoriasis. The UK Biobank does not only collected information on participants' comorbidities at baseline but collect this information through linkages with NHS hospital episode statistics, mortality and cancer registrations.[6] Further follow-up of the UK Biobank will be able to gather greater insights on the incidence of new comorbidities. Thus, it is likely to be an important population database for assessing the temporal relationship between psoriasis and comorbidities and for other common dermatological disorders too.

Psoriasis patients were more likely to have comorbidities as mentioned in Chapter 4. Thus, they tend to use multiple medications. The UK Biobank collected medication use from the participants. It may be used to examine patterns of polypharmacy and risk of adverse drug reactions in patients with psoriasis. In addition, the UK Biobank has collected information on phenotypic and genotypic data, it may be used to investigate genes relating to the associations between psoriasis and comorbidities. This could be used to gain a better understanding of the mechanisms between psoriasis and its comorbidities.

Recently, biologic therapies have an increasing role in the management of psoriasis and more biologic therapies have recently been marketed. Specifically, some biologic therapies [e.g. brodalumab (anti-IL-17RA agent) and guselkumab (anti-IL-23 agent)] have been approved for the treatment of psoriasis after the studies of this thesis were completed. There is a need to conduct research examining the impact of these medicines on the risk of major CVEs in patients with psoriasis. This will ensure the safety of these products.

The BADBIR has recruited patients exposed to biosimilar products for the treatment of psoriasis. This thesis did not evaluate biosimilars because there was no patient receiving biosimilar products who met the inclusion criteria for the study. Owing to their lower costs relative to the originators, they will be increasingly used in the future. It is essential to assess whether their

cardiovascular safety profiles are similar to those of the innovator biologic therapies as well as the risk of other serious AEs.

The prospective cohort study in this thesis examined the risk of major CVEs in psoriasis patients exposed to the first biologic therapies for about two years in the BABDIR (Chapter 6). However, biologic therapies may take longer to have an effect on the risk of major CVEs. This may change the conclusions of the cohort study in the future as additional data matures. In addition, patients with psoriasis were more likely to have cardiovascular risk factors and MI as described in Chapter 4. Thus, some patients with psoriasis receiving biologic therapies might have a history of CVEs. It will be important to conduct future prospective cohort studies with more patients, longer follow-up and additional data on cardiovascular risk factors and the history of medication use to examine the effect of biologic therapies on the risk of the first or recurrent CVEs; or other CVEs (such as heart failure) in patients with psoriasis. These studies would provide important information on the cardiovascular safety profile of biologic therapies in longer-term real-life practice. These will help healthcare professionals, researchers, patients and policy makers to better understand the safety profiles of these innovative biologic therapies.

7.4 Final conclusions

In conclusion, the cross-sectional study presented in the thesis was the first to examine demographic and anthropometric characteristics of patients with psoriasis and prevalence of physical and mental health comorbidities using the UK Biobank. This database was designed to support a diverse range of research so as to improve the prevention, diagnosis and treatment of serious and life-threatening diseases among middle and old aged people.[353] Thus, it is an invaluable source for psoriasis studies. The results of the cross-sectional study showed that patients with psoriasis had an increased risk of a number of physical and mental health comorbidities compared to participants without psoriasis. In particular, cardiovascular risk factors e.g. hypertension, a history of MI and peripheral vascular disease, high cholesterol, diabetes and psoriatic arthritis or rheumatoid arthritis were increased.

The impact of biologic therapies on the risk of major CVEs was examined by the largest systematic review and meta-analysis of RCTs conducted to date and the first large prospective cohort study comparing the risk between biologic therapies using the BADBIR dataset (registry data). The results showed that there was no significant difference in the risk of MACEs in psoriasis patients treated with biologic therapies compared with placebo or the different doses of the same biologic therapies. Moreover, no significant difference in the risk of major CVEs was observed in patients treated with biologic therapies compared with different biologic therapies or methotrexate.

Future larger, longer follow-up studies with robust study designs are still required to examine the temporal relationship between psoriasis and comorbidities and the impact of biologic therapies on the risk of major CVEs over the longer-term.

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Appendices

Appendix 1: Biobank ethic approval

NHS
Health Research Authority

North West - Haydock Research Ethics Committee
3rd Floor - Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0207 104 8012

13 May 2016

Dr Tim Peakman
UK Biobank Limited
1-4 Spectrum Way
Adswood
Stockport
Cheshire
SK3 0SA

Dear Dr Peakman

Title of the Research Tissue Bank:	**UK Biobank: a large scale prospective epidemiological resource**
REC reference:	**16/NW/0274**
Designated Individual:	**Dr Tim Peakman**
IRAS project ID:	**200778**

The Research Ethics Committee reviewed the above application at the meeting held on 10 May 2016. Thank you for attending with Mr Jonathan Sellors and Ms Nicola Doherty to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Ms Rachel Katzenellenbogen, nrescommittee.northwest-haydock@nhs.net.
Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Favourable opinion

The members of the Committee present gave a favourable ethical opinion of the above research tissue bank on the basis described in the application form and supporting documentation, subject to the conditions specified below.

The Committee has also confirmed that the favourable ethical opinion applies to all research

projects conducted in the UK using tissue or data supplied by the tissue bank, provided that the release of the tissue or data complies with the attached conditions. It will not be necessary for these researchers to make project-based applications for ethical approval. They will be deemed to have ethical approval from this committee. You should provide the researcher with a copy of this letter as confirmation of this. The Committee should be notified of all projects receiving tissue and data from the tissue bank by means of an annual report.

This application was for the renewal of a Research Tissue Bank application. The previous REC Reference number for this application was 11/NW/0382.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Research governance

Under the Research Governance Framework (RGF), there is no requirement for NHS research permission for the establishment of research tissue banks in the NHS. Applications to NHS R&D offices through IRAS are not required as all NHS organisations are expected to have included management review in the process of establishing the research tissue bank.

Research permission is also not required by collaborators at tissue collection centres (TCCs) who provide tissue or data under the terms of a supply agreement between the organisation and the research tissue bank. TCCs are not research sites for the purposes of the RGF.

Research tissue bank managers are advised to provide R&D offices at all TCCs with a copy of the REC application for information, together with a copy of the favourable opinion letter when available. All TCCs should be listed in Part C of the REC application.

NHS researchers undertaking specific research projects using tissue or data supplied by the research tissue bank must apply for permission to R&D offices at all organisations where the research is conducted, whether or not the research tissue bank has ethical approval.

Site-specific assessment (SSA) is not a requirement for ethical review of research tissue banks.

Summary of discussion at the meeting

Social or scientific value; scientific design and conduct of the study

The Committee were pleased to see that UK Biobank was constantly re-evaluating itself with regards to new technology and data collection. This meant that new tests were undertaken and new data and tissue collected allowing UK Biobank to grow and develop as a resource.

The Committee were very pleased that this resource was open access and also that researchers had to register to use it. The Committee noted that while UK Biobank owned the resource they had no preferential access. The Committee very happy to note that all research results had to be sent back to UK Biobank as part of a transparency agenda.

The Committee noted that the data was being used by a broad range of researchers and asked how use would be maximised in the future.

> You explained that originally UK Biobank had been designed to be used in case control studies. However, you had been able to demonstrate that centralised generation of large datasets had advantages of cost, standardisation and a lack of gaps. This meant that it was being used in more than just case control studies.
>
> You said that genotyping was being done on all participants and that they were currently measuring 34 biomarkers with the data available to all. You said that you were currently working up a proposal to measure 40 markers of infectious disease and were also looking at developing strategies to look at proteins and metabolites. You said it was important to maximise the tissue so that, for example, you wouldn't use tissue simply to measure glucose, but if you could run tests that delivered a lot of data, including glucose, then the data would be gathered in a good way.
>
> You said that the data was linked to various registers, including deaths, cancer and hospital visit. 30% of English participants had primary care information and this was a lot higher for Welsh and Scottish participants. This meant that you would be able to create a plausible calendar as to when the data would be mature for more common conditions and then you would put out a call for researchers.

The Committee noted that one of the criteria for accessing the biobank was that the research be "in the public interest". The Committee asked if any applications had been turned down because they had not been in the public interest.

> You said that no applications had been turned down because they were not in the public interest. In fact, only 2 or 3 requests for samples had been turned down and that was because they had either requested too much or actually did not need to turn to a biobank to do their research.

The Committee agreed that it had been an exemplary submission and had led to an interesting and informative discussion. The Committee looked forward to the publication regarding imaging and the reporting of findings and hoped the researchers would advise them of when it was published and how it could be accessed.

Care and protection of research participants: respect for potential and enrolled participants' welfare and dignity

The Committee agreed that the systems in place to avoid identifying participants were robust. Always growing and considering and developing.

The Committee noted that UK Biobank was regularly in touch with participants via newsletter and held an Annual General Meeting. The Committee agreed this was very important if participants were to stay motivated and interested as without this no new data or tissue could be added.

The Committee noted that the imaging Participant Information Sheet and consent form said that GPs would be contacted if anything clinically significant was discovered. The Committee noted that UK Biobank had had a policy of not feeding back findings and wondered if this policy had now changed. The Committee also agreed that they needed to know more about how significant

clinical findings were determined. For example, carotid arteries narrowed as people aged, so would all narrowing be reported or just ones with a certain percentage of narrowing.

The Committee asked what the current position was regarding feeding back clinically significant findings.

> You said that the position had not changed, although it was reconsidered on a regular basis. When participants came for their baseline visit in 2007-2010 if something was spotted during the visit, then it was fed back. However, assay or other research findings were not fed back.
>
> With regard to imaging, which could lead to acute findings such as cancer, you explained that you had spent 5-6 years working out the best protocol for that. The end result was that if the radiographer observed something that concerned them it was flagged and a radiologist would assess it. If the radiologist determined that it was significant then it was reported to the GP.
>
> You explained that during the imaging pilot you had run two protocols, the one that is in current use, and a second one that involved a radiologist screening all of the images. After follow up it became clear that this was hugely problematic, not because of cost or expediency, but because it had led to 200 false positives. At the extreme end there had been a lung section and a removal of ovaries for people with false positives. Scaling this up to 100,000 people meant there could be 20,000 false positives.
>
> You said that you had spoken to participants and to imaging projects and it had been agreed that while the radiographers might miss things, the best protocol was to have radiologists only look at images flagged by radiographers. You also said that you would be publishing the results of this research shortly.
>
> You said that, in short, the feedback policy was that anything of clinical significance discovered during data acquisition would be fedback but any other findings would not be.

The Committee agreed that this was acceptable, especially as it was all made very clear to participants in information sheets.

The Committee asked why radiologists were diagnosing so many false positives.

> You said that the images were research scans which, despite what many participants had thought, were not more detailed than ones taken for clinical purposes. Additionally, the radiologists did not have any of the other information they would have in normal diagnosis.

The Committee agreed that the level of commitment required from participants was high and the Committee agreed they would like to know how many participants had withdrawn and how many had simply been lost to contact. However, the Committee was impressed with the way UK Biobank kept participants informed of new developments and asked how many participants had been lost to contact or withdrawal.

> You said that just over 1,000 participants had withdrawn with about 600 of them having requested all tissue and data be removed from the resource. The Committee said that

while annual communications always sparked some withdrawals, the benefits of the communication far outweighed that problem.

You said that most communication was by email, including web based questionnaires. However, it was easier to keep in touch with people by post because if they moved you could usually find their new address. Also it was impossible to know how many emails were opened and read, so no one knew who actually read the newsletter.

You explained that response rates to questionnaires had actually gone up over time and that there had been a 50% response rate to the request for participants willing to wear an accelerometer. In fact, you had managed to recruit 100,000 participants to do that.

You said that you were now also starting to use mobile technology to contact participants.

Other ethical issues were raised and resolved in preliminary discussion before your attendance at the meeting.

Duration of ethical opinion

The favourable opinion is given for a period of five years from the date of this letter and provided that you comply with the standard conditions of ethical approval for Research Tissue Banks set out in the attached document. You are advised to study the conditions carefully. The opinion may be renewed for a further period of up to five years on receipt of a fresh application. It is suggested that the fresh application is made 3-6 months before the 5 years expires, to ensure continuous approval for the research tissue bank.

Research Tissue Bank Renewals

The Research Tissue Bank has been renewed for a further five years from the end of the previous five year period. The previous five year period ran from 17 June 2011 to 17 June 2016. This Research Tissue Bank may be renewed for further periods of five years at a time by following the process described in the above paragraph.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Human Tissue Authority licence [HTA Licence 12002 & 12624]		26 July 2010
IRAS Checklist XML [Checklist_27042016]		27 April 2016
Other [Table 1: Comparison of the sample collection for the baseline assessment and imaging pilot]	1.0	02 March 2016
Other [Table 2: Progress with key cohort-wide linkages Q1-2 2016]	1.0	02 March 2016
Other [UK Biobank Ethics & Governance Framework]	3.0	01 October 2007
Other [Figure 1: Submitted Access Applications by areas of interest]	1.0	02 March 2016
Other [Table 3: Biochemistry assays being performed in all 500,000 participants]	1.0	02 March 2016
Other [Participant Withdrawal Form]	1.1	10 February 2012

Other [UK Biobank Newsletter June 2015]	1.0	22 June 2015
Other [Data Dictionary Showcase Sept15]	Sept 2015	24 March 2016
Other [Curriculum vitae - Timothy Peakman]	March 2016	24 March 2016
Other [RTB Report March 2016]	1.0	24 March 2016
Other [Appendix: Occupational Questionnaire]	1.0	27 August 2014
Other [Appendix: Occupational Questionnaire Invitation Text]	1.0	27 August 2014
Other [Appendix: Occupational Questionnaire Reminder Invitation Text]	1.0	27 August 2014
Other [Revised Imaging Invitation Email]	1.0	06 October 2014
Other [Imaging Reminder Text & SMS]	1.0	18 November 2014
Other [Feedback in the UK Biobank Imaging pilot study]	Jan 2014	29 January 2014
Other [Invitation letter for deliberative group interviews]	1.0	06 October 2014
Other [Imaging 2nd Invite email HTML]	0.1	01 January 2016
Other [Imaging 2nd Invite email PLAIN]	0.2	01 January 2016
Other [Imaging Participant pre-screening questionnaire]	1.3	27 October 2015
Other [Imaging Exit Survey]	0.1	01 January 2016
Other [Invite email reminder 6-month questionnaire HTML]	0.1	01 October 2015
Other [Invite email reminder 6-month questionnaire PLAIN]	0.1	01 October 2015
Other [Invite email reminder 6-week questionnaire HTML]	0.1	01 October 2015
Other [Invite email reminder 6-week questionnaire PLAIN]	0.1	01 October 2015
Other [Invite email reminder understanding consent questionnaire HTM]	0.1	01 October 2015
Other [Invite email reminder understanding consent questionnaire PLAIN]	0.1	01 October 2015
Other [Appendix 1: Mental Health Questionnaire]	1.2	23 March 2016
Other [Appendix 2: Rationale and tools used in Mental Health Questionnaire]	1.1	04 March 2016
Other [Appendix 3: Invitation email Mental Health Questionnaire]	1.2	11 March 2016
Other [Appendix 4: Reminder email Mental Health questionnaire]	1.2	11 March 2016
Other [Appendix 5: Reminder partial responder email Mental Health questionnaire]	1.1	11 March 2016
Other [Appendix 6: Last chance email Mental Health questionnaire]	1.0	11 March 2016
Other [Repeat Assessment email invitation]	1.0	09 August 2012
Other [Repeat Assessment invite letter]	1.0	26 March 2012
Other [Repeat Assessment confirmation letter]	1.0	11 July 2012
Other [Confirmation of imaging appointment letter]	1.0	08 April 2016
Other [Activity Monitor Information Letter]	26/03/2012	26 March 2012
Other [Activity Monitor Invitation Letter]	26/03/2012	26 March 2012
Other [Activity Monitor Return Reminder]	26/03/2012	26 March 2012
Other [UK Biobank Assessment form]	20061124	24 November 2006
Other [Diet Questionnaire]	1.0	11 April 2016
Other [UK Biobank Participant Invite letter]	1.0	11 April 2016
Other [Touch-screen questionnaire]	1.0	11 April 2016

Other [Touch-screen questionnaire addendum]	1.0	11 April 2016
Other [Cognitive Function tests]	1.0	26 March 2013
Other [Cognitive Function Web Questionnaire email invitation]	1.0	26 March 2013
Other [Cognitive Function Web Questionnaire email reminder]	1.0	26 March 2013
Other [Cognitive Function Web Questionnaire email reminder partial responder]	1.0	26 March 2013
Other [UK Biobank Protocol]	21/03/2007	21 March 2007
Other [UK Biobank Protocol addendum 1]	09/04/2009	09 April 2009
Other [UK Biobank Protocol addendum 2]	02/07/2009	02 July 2009
Other [Text Message to request email address]	1.0	20 April 2016
Other [UK Biobank TIME study invitation]	2.2	15 April 2016
Other [Imaging Questionnaire to assess participant understanding of consent]	January 2014	01 January 2014
Other [Imaging Participant Questionnaire sent at 6 weeks to assess IF]	January 2014	01 January 2014
Other [Imaging Participant Questionnaire sent at 6 months to assess impact of IF]	January 2014	01 January 2014
Other [Imaging Questionnaire sent to participants who did not receive IF feedback]	January 2014	01 January 2014
Other [Imaging Letters notifying participant and participant's GP of potentially serious incidental finding]	1.0	01 January 2014
Other [Imaging GP questionnaire sent at 6 months to assess the later impact of feedback of IF]	1.0	01 April 2015
Participant consent form [UK Biobank Consent form]	20061124	24 November 2006
Participant consent form [Consent Form for the imaging assessment: UK Biobank]	Jan 2014	29 January 2014
Participant information sheet (PIS) [Participant Information Leaflet]	21/04/2010	21 April 2010
Participant information sheet (PIS) [Biobank Imaging Information Leaflet]	Dec 2015	01 December 2015
Participant information sheet (PIS) [Repeat Assessment Participant Information Leaflet]	26/03/2012	26 March 2012
Participant information sheet (PIS) [Further Information Leaflet]	001	08 April 2016
Participant information sheet (PIS) [Biobank Imaging Information Leaflet including ECG monitoring]	2.0	26 November 2014
Protocol for management of the tissue bank [UK Biobank Access Procedures]	1.0	01 November 2011
REC Application Form [RTB_Form_24032016]		24 March 2016

Licence from the Human Tissue Authority

Thank you for providing a copy of the above licence.

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet. Dr Tim Sprosen helped set up UK Biobank and was a member of the Scientific Steering Committee. It was agreed that Dr Sprosen would leave the room during the discussion and take no part in the discussion or decision making. Dr Valerie Siddall, Alternate Vice-Chair, would chair

that portion of the meeting.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached standard conditions give detailed guidance on reporting requirements for research tissue banks with a favourable opinion, including:

- Notifying substantial amendments
- Submitting Annual Progress reports

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

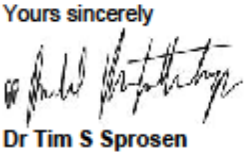
The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/NW/0274	**Please quote this number on all correspondence**

Yours sincerely



Dr Tim S Sprosen
Chair

E-mail: nrescommittee.northwest-haydock@nhs.net

Enclosures:	List of names and professions of members who were present at the meeting and those who submitted written comments
	Standard approval conditions

North West - Haydock Research Ethics Committee

Attendance at Committee meeting on 10 May 2016

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mrs Moyra Ann Baldwin	Retired Senior Lecturer - Oncology	Yes	
Mr Stephen Edgar	Designer	Yes	
Dr Michael U Eshiett	Consultant Physician in Neurological Rehabilitation	No	
Mr Simon Hill	Pharmacist	No	
Dr Ben Johnson	Consultant Psychiatrist	No	
Dr Ezzat Kozman	Consultant Gynaecologist	Yes	
Mr Charles Otim	Research Support Officer	Yes	
Dr David Pilling	Consultant Radiologist	Yes	
Miss Anna Sekula	Nurse	No	
Dr Valerie E Siddall	Retired Senior Manager - Pharmaceutical Industry	Yes	Alternate Vice-Chair – Meeting Chair for this application
Dr Tim S Sprosen	Epidemiologist	Yes	Chair
Dr Zhe Wang	Medical Statistician	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Ms Rachel Katzenellenbogen	REC Manager

CONDITIONS OF ETHICAL APPROVAL

Research Ethics Committee:	North West - Haydock Research Ethics Committee
Research Tissue Bank:	UK Biobank: a large scale prospective epidemiological resource
REC reference number:	16/NW/0274
Name of applicant:	Dr Tim Peakman
Date of approval:	10 May 2016
IRAS project ID:	200778

Ethical approval is given to the Research Tissue Bank ("the Bank") by the Research Ethics Committee ("the Committee") subject to the following conditions.

1. Further communications with the Committee

1.1 Further communications with the Committee are the personal responsibility of the applicant.

2. Duration of approval

2.1 Approval is given for a period of 5 years, which may be renewed on consideration of a new application by the Committee, taking account of developments in legislation, policy and guidance in the interim. New applications should include relevant changes of policy or practice made by the Bank since the original approval together with any proposed new developments.

3. Licensing

3.1 A copy of the Licence from the Human Tissue Authority (HTA) should be provided when available (if not already submitted).

3.2 The Committee should be notified if the Authority renews the licence, varies the licensing conditions or revokes the Licence, or of any change of Designated Individual. If the Licence is revoked, ethical approval would be terminated.

4. Generic ethical approval for projects receiving tissue

4.1 Samples of human tissue or other biological material may be supplied and used in research projects to be conducted in accordance with the following conditions.

4.1.1 The research project should be within the fields of medical or biomedical research described in the approved application form.

4.1.2 The Bank should be satisfied that the research has been subject to scientific critique, is appropriately designed in relation to its objectives and (with the exception of student research below doctoral level) is likely to add something useful to existing knowledge.

4.1.3 Where tissue samples have been donated with informed consent for use in future research ("broad consent"), the Bank should be satisfied that the use of the samples complies with the terms of the donor consent.

4.1.4 All samples and any associated clinical information must be non-identifiable to the researcher at the point of release (i.e. anonymised or linked anonymised).

4.1.5 Samples will not be released to any project requiring further data or tissue from donors or involving any other research procedures. Any contact with donors must be confined to ethically approved arrangements for the feedback of clinically significant information.

4.1.6 A supply agreement must be in place with the researcher to ensure storage, use and disposal of the samples in accordance with the HTA Codes of Practice, the terms of the ethical approval and any other conditions required by the Bank.

4.2 A research project in the UK using tissue provided by a Bank in accordance with these conditions will be considered to have ethical approval from the Committee under the terms of this approval. In England, Wales and Northern Ireland this means that the researcher will not require a licence from the Human Tissue Authority for storage of the tissue for use in relation to this project.

4.3 The Bank may require any researcher to seek specific ethical approval for their project. Such applications should normally be made to the Committee and booked via the Central Booking System

4.4 A Notice of Substantial Amendment should be submitted to seek the Committee's agreement to change the conditions of generic approval.

5. Records

5.1 The Bank should maintain a record of all research projects to which tissue has been supplied. The record should contain at least the full title of the project, a summary of its purpose, the name of the Chief Investigator, the sponsor, the location of the research, the date on which the project was approved by the Bank, details of the tissue released and any relevant reference numbers.

5.2 The Committee may request access to these records at any time.

6. Annual reports

6.1 An annual report should be provided to the Committee listing all projects for which tissue has been released in the previous year. The list should give the full title of each project, the name of the Chief Investigator, the sponsor, the location of the research and the date of approval by the Bank. The report is due on the anniversary of the date on which ethical approval for the Bank was given.

6.2 The Committee may request additional reports on the management of the Bank at any time.

7. Substantial amendments

7.1 Substantial amendments should be notified to the Committee and ethical approval sought before implementing the amendment. A substantial amendment generally means any significant change to the arrangements for the management of the Bank as described in the application to the Committee and supporting documentation.

7.2 A Notice of Substantial Amendment should be generated by accessing the original application form on the Integrated Research Application System (IRAS).

7.3 The following changes should always be notified as substantial amendments:

7.3.1 Any significant change to the policy for use of the tissue in research, including changes to the types of research to be undertaken or supported by the Bank.

7.3.2 Any significant change to the types of biological material to be collected and stored, or the circumstances of collection.

7.3.3 Any significant change to informed consent arrangements, including new/modified information sheets and consent forms.

7.3.4 A change to the conditions of generic approval

7.3.5 Any other significant change to the governance of the RTB.

8. Serious Adverse Events

8.1 The Committee should be notified as soon as possible of any serious adverse event or reaction, any serious breach of security or confidentiality, or any other incident that could undermine public confidence in the ethical management of the tissue. The criteria for notifying the Committee will be the same as those for notifying the Human Tissue Authority in the case of research tissue banks in England, Wales and Northern Ireland.

9. Other information to be notified

9.1 The Committee should be notified of any change in the contact details for the applicant or where the applicant hands over responsibility for communication with the Committee

to another person at the establishment.

10. Closure of the Bank

10.1 Any plans to close the Bank should be notified to the Committee as early as possible and at least two months before closure. The Committee should be informed what arrangements are to be made for disposal of the tissue or transfer to another research tissue bank.

10.2 Where tissue is transferred to another research tissue bank, the ethical approval for the Bank is not transferable. Where the second bank is ethically approved, it should notify the responsible Research Ethics Committee. The terms of its own ethical approval would apply to any tissue it receives.

11. Breaches of approval conditions

11.1 The Committee should be notified as soon as possible of any breach of these approval conditions.

11.2 Where serious breaches occur, the Committee may review its ethical approval and may, exceptionally, suspend or terminate the approval.

Appendix 2: UK Biobank information leaflet

biobank uk

Improving the health of future generations

INFORMATION LEAFLET

You are being invited to take part in a major medical research project called "UK Biobank". The purpose of UK Biobank is to set up a resource that can support a diverse range of research intended to improve the prevention, diagnosis and treatment of illness, and the promotion of health throughout society.

Before you decide whether to join, it is important for you to understand why UK Biobank is being done and what is involved. Please take the time to read the following information carefully, and discuss it with others if you wish.

If anything is not clear, or if you would like more information, please telephone free of charge on 0800-0-276-276 to talk to a member of the project team. More information about UK Biobank is also available at www.ukbiobank.ac.uk. At the assessment visit, there will be a further opportunity to ask any questions that you might have.

Thank you for taking the time to consider taking part in UK Biobank.

Contact details:

UK Biobank
1-2 Spectrum Way
Adswood
Stockport
Cheshire
SK3 0SA
Email: ukbiobank@ukbiobank.ac.uk
Freephone: 0800-0-276-276

What is the purpose of UK Biobank?

UK Biobank aims to study how the health of 500,000 people, currently aged 40-69, from all around the UK is affected by their lifestyle, environment and genes. The purpose of this major project is to improve the prevention, diagnosis and treatment of a wide range of illnesses (such as cancer, heart disease, diabetes, dementia, and joint problems) and to promote health throughout society.

By analysing answers, measurements and samples collected from participants, researchers may be able to work out why some people develop particular diseases while others do not. This should help us to find new ways to prevent early death and disability from many different diseases.

Like giving blood for transfusions, UK Biobank is not intended to help directly those who take part – but it should give future generations a much better chance of living their lives free of diseases that disable and kill.

How have I been chosen for invitation into UK Biobank?

People to invite are identified from National Health Service (NHS) records. The only information used, in confidence, for this purpose is your name, address, sex, date of birth, NHS/CHI number and general practice. These details are processed centrally on behalf of the NHS in accordance with the Data Protection Act.

Your date of birth has allowed us to check that you are aged between 40 and 69 years. We have also been able to advise your general practice that their patients are being invited to take part.

We do not know anything else about you, and have not seen any of your medical records. Only if you attend the UK Biobank assessment visit and give your written consent would UK Biobank be able to access your medical records. (All such information would be held in strict confidence).

It is important that all types of people join UK Biobank. We would like you to take part whether you are in good health or have health problems, and whether you have a disability or may require help reading questions during the assessment visit. If you would welcome extra assistance to attend the assessment centre, or want to alert us to anything else beforehand, please telephone on 0800-0-276-276.

What does taking part in UK Biobank involve?

Taking part in UK Biobank would involve you in:

- Attending a local assessment centre for about 2 to 3 hours to answer some simple questions, to have some standard measurements and to give small samples of blood, saliva and urine.
- Agreeing to allow your health to be followed for many years by UK Biobank directly through routine medical and other health-related records.
- Being re-contacted by UK Biobank (e.g. to answer some more questions and/or to attend another assessment visit), although this would be entirely optional.
- Agreeing to have your samples and health-related information stored by UK Biobank and used in an anonymised form by researchers for many years.

What happens DURING the assessment visit?

The appointment at the assessment centre should take about 2 to 3 hours. During this visit, you would:

- Learn more about UK Biobank, and have the chance to ask any questions that you might have before deciding whether to join.
- Answer questions on your health, lifestyle and diet, memory, work and family history.
- Have non-invasive measurements of blood pressure, pulse rate, height, weight, body fat, vision, fitness, grip strength, bone density and lung function.
- Give small samples of blood (about 3 tablespoons) saliva and urine for long-term storage and analysis (including genetic data).
- Receive information about the key results of your measurements (see above), although the visit is not intended to be a "health check". (None of your individual results will be released to your doctor or anyone else).

  Note: If, for any reason, you might not be able to undergo some of the physical measurements described above then you can still take part.

What happens AFTER the assessment visit?

For many years after the assessment visit, UK Biobank would follow the health of everyone who agrees to take part through their full medical records and other records that may be related to health (e.g. occupational or residential information).

Your blood, saliva and urine samples will not generally be analysed immediately following collection. Instead, during follow-up over the next few decades, your stored samples will be analysed for approved health-related research.

At some time in the future, participants might be re-contacted by UK Biobank and asked more questions, although giving such additional help would be entirely optional. Similarly, some participants might be asked in later years to attend another assessment visit (including questions, measurements and samples), although again attendance at such visits would be optional.

All of your personal information would be held by UK Biobank in strict confidence with careful controls, and no identifiable information about participants would be available to anyone outside of UK Biobank.

What should I do if I want to take part?

If you would like to attend your local assessment centre to find out more about UK Biobank and possibly take part, then you will need to confirm your appointment.

You can do this most easily by **telephoning us (Mon-Sat; 8.00am to 7.00pm) free of charge on 0800-0-276-276:** if the appointment on your invitation letter is not convenient then you can change it easily during this call. Alternatively, you can let us know that the appointment on the letter is convenient by completing and returning the reply-paid form provided with your invitation letter or visiting the study website at www.ukbiobank.ac.uk.

In most assessment centres appointments are available Monday to Friday from 8.00am to 7.00pm and Saturday from 8.00am to 5.00pm. Please let us know if you have any special needs to help you get into the assessment centre (e.g. wheelchair access) or if you need any special assistance when you arrive (e.g. have poor vision or are hard of hearing).

What should I do if I do not want to take part?

If you definitely do not want to take part then we would be grateful if you would indicate this on the pre-paid reply form and return it to us. Alternatively, you can telephone us on 0800-0-276-276 or visit www.ukbiobank.ac.uk. Letting us know that you will not be attending will allow us to give someone else the appointment.

What can I do if I'm unsure about taking part?

More details about UK Biobank are given in the remainder of this information leaflet. If this does not answer all of your questions then please telephone us free of charge on 0800-0-276-276 (Mon-Sat; 8.00am to 7.00pm) and ask for more information. Alternatively, if you can access the internet (perhaps at home, work or in the local library), more details are available at www.ukbiobank.ac.uk.

At the start of the assessment visit, there will be a further opportunity to ask any questions that you still have about participation. Attending for this assessment does not commit you to taking part.

Do I need to do anything BEFORE the assessment visit?

The main thing to do is confirm your attendance at the assessment centre for a day and time that is convenient for you. We shall then send written confirmation of your booked appointment. In addition, a short pre-visit questionnaire will be included so that you can make a note about certain things that you might not otherwise remember:

- All medications, vitamins or supplements that you are taking regularly.
- All operations that you have had at any time in the past.
- Serious medical conditions that seem to run in your family.
- Your birthweight, whether breastfed, and place of birth (if known).

Can I claim travel expenses?

Yes; you can claim back any reasonable travel expenses at the end of the visit by completing a simple claim form (it would be helpful if you kept any receipts). If you have any questions about travel expenses, please telephone us on 0800-0-276-276 (Mon-Sat; 8.00am to 7.00pm).

How do I prepare for the assessment visit?

When you attend your assessment appointment, please:

- Bring your completed pre-visit questionnaire, and the directions for the assessment centre so that you don't have difficulties finding it.
- Bring any reading glasses that you use as you will need to be able to read clearly from a computer screen (if you normally wear contact lenses it would be easier for the eye test if you could wear your glasses for the visit).
- Wear light loose-fitting clothing and, if possible, avoid wearing stockings or tights to make some of the measurements easier (e.g. those needing bare feet).
- Be prepared to spend about 2 to 3 hours in the assessment centre.

Do I have to take part in UK Biobank?

No; it is entirely up to you to decide whether or not to help with this project. If you do decide to take part you will be asked to sign a consent form during the assessment visit.

Why do you need my written consent?

Your participation in UK Biobank is entirely voluntary. By signing the consent form, you would be confirming your willingness to take part. In particular, you would be agreeing to:

- Answer some questions and have some measurements.
- Give blood, saliva and urine for long-term storage and any testing (including obtaining genetic information and storing white blood cells so more DNA can be made).
- Allow UK Biobank to have long-term access to your existing and future medical and other health-related records.
- Be contacted again in the future by UK Biobank.

Even if you do consent to participate, you would be free to withdraw at any time later if you wished to do so (see below). The UK Biobank resource will be most valuable if few people withdraw, so please inform the assessment centre staff if you have any concerns with what taking part might involve.

Do I need to agree to everything?

No. If you feel uncomfortable about answering certain questions then you do not need to answer them. Similarly, if you do not want to have certain health measures, or to give a urine or saliva sample, then tell the staff.

We do, however, need your agreement to take a blood sample, which will be stored and used for tests (including genetic ones) in approved research. It will not be possible for you to give permission for some, but not other, types of research. We also need your permission to access your medical and other health-related records in confidence for many years (even if you lose mental capacity or die). So, if you don't wish to agree to these parts of UK Biobank, you will not be able to join.

Are there any risks for me in joining UK Biobank?

Taking part in UK Biobank should not cause you any harm. The project aims to observe what happens to participants over the next few decades so that future generations can benefit. It is not intended to change directly what happens to people who take part: in particular, the initial assessment visit is not a "health check". Apart from providing you with the results of some standard measurements made during that visit, none of your results will be given to you or your doctors (even if the results do not seem to be normal).

This is because such feedback outside of the normal clinical setting is of questionable value, and might even be harmful (for example, causing undue alarm and having potentially adverse effects on insurance status), especially when given without prior counselling or support. For further details on this topic, please call 0800-0-276-276 or look on our website at www.ukbiobank.ac.uk.

It is possible that you may be slightly uncomfortable with some of the questions asked, or measurements made, during the assessment visit. You will generally be able to skip such questions or measures. You may feel some discomfort when you have blood taken, although our staff are specially trained to reduce this risk.

Participation involves a minimal risk in relation to the use of personal information. Great care will be taken to ensure the confidentiality of all data (see below) and the risk to participants of a breach of confidentiality is considered very low.

Over the coming years, a very wide range of tests will be done on your blood, saliva and urine samples for approved medical and other health-related research. Details that might identify you will be removed from any information and samples provided to researchers in order that they cannot be traced back to you. None of your particular test results will be fed back to you, your doctors or anyone else. So, taking part should not have any adverse effects on you (including your employment status or ability to get insurance).

How will information about me be kept confidential?

UK Biobank has put a number of rigorous procedures in place to protect the confidentiality of participants. These include:

- Keeping information that might identify individuals (such as name and address) separate in UK Biobank's databases from other information about participants.
- Computer security to block unauthorised access (for example, by "hackers") to the computers that hold personal information.
- Access to personal information is restricted within UK Biobank, and all staff sign confidentiality agreements as part of their employment contracts.
- Data or samples provided to researchers will not include personal identifying details.

This should prevent identifiable information from being used – inadvertently or deliberately – for any purpose other than to support the project.

Who will be able to use my information and samples?

Information and samples from UK Biobank participants will be available only to researchers who have relevant scientific and ethics approval for their planned research. This could include researchers who are working in other countries and in commercial companies looking for new treatments.

Results from any tests made on participants or their samples will be put in the UK Biobank database so that they are available to all approved researchers. There will also be a requirement to publish the results of all research based on the resource so that people can benefit from it.

Insurance companies and employers will not be given any individual's information, samples or test results, and nor will we allow access to the police, security services, relatives or lawyers, unless forced to do so by the courts.

Results of research conducted on the UK Biobank resource will be made available to participants, and anyone else who might be interested, at www.ukbiobank.ac.uk.

How do I withdraw if I want to do so?

UK Biobank will be most valuable if few people do withdraw from it, so potential participants are asked to discuss any concerns that they might have with a member of the project team before agreeing to participate.

During the assessment visit, you can withdraw at any time after giving your signed consent, by telling one of the staff. You will be asked to confirm your withdrawal with a signature.

After the visit, you can withdraw by telephoning us on 0800-0-276-276 (Mon-Sat; 8.00am to 7.00pm) or by writing to the coordinating centre office. This would allow us to discuss your concerns with you and to determine the desired level of withdrawal from the following options:

- *"No further contact"*: This means that UK Biobank would no longer contact you directly, but would still have your permission to retain and use information and samples provided previously and to obtain and use further information from your health records.
- *"No further access"*: This means that UK Biobank would no longer contact you or obtain further information from your health records in the future, but would still have your permission to use the information and samples provided previously.
- *"No further use"*: This means that, in addition to no longer contacting you or obtaining further information about you, any information and samples collected previously would no longer be available to researchers. UK Biobank would destroy your samples (although it may not be possible to trace all distributed sample remnants) and would only hold your information for archival audit purposes. Your signed consent and withdrawal would be kept as a record of your wishes. Such a withdrawal would prevent information about you from contributing to further analyses, but it would not be possible to remove your data from analyses that had already been done.

If, having discussed the options and your concerns, you did decide to withdraw then we would send you a Withdrawal Form to confirm your wishes in writing. This form can be completed by you or, if you are not able to do so for some reason (such as illness), by someone able to act on your behalf.

Who is organising and funding UK Biobank?

UK Biobank has been set up by the Department of Health, Medical Research Council and Scottish Government, and by the Wellcome Trust medical charity. It is also supported by the Welsh Assembly Government, by health research charities (such as the British Heart Foundation, Cancer Research UK and Arthritis Research Campaign) and by the National Health Service.

UK Biobank is a not-for-profit charitable company set up to act as the legal owner and guardian of the database and sample collection. In signing the consent form, participants transfer all property and intellectual property rights in their samples and data to UK Biobank. The charity's role is to protect this valuable resource so that scientists can do a wide range of health-related research in the future.

UK Biobank collaborates with scientists from more than 20 British Universities who have developed its design. These plans have been reviewed by an independent group of international scientists and approved by the NHS North West Research Ethics Committee. In addition, the independent Ethics and Governance Council will monitor the development and use of the resource (for more information, see www.egcukbiobank.org.uk).

What happens if something goes wrong?

The risks of participants suffering harm as a result of taking part are minimal, and UK Biobank has insurance in place to provide compensation for any negligent harm caused by participation.

Who do I contact if I have any concerns?

If you have any concerns or complaints about anything to do with UK Biobank then you can telephone us free of charge on 0800-0-276-276 (Mon-Sat; 8.00am to 7.00pm) and ask to speak directly to one of the organisers. Alternatively, if you would like to write to the person in charge, please send your letter to:

Professor Rory Collins
UK Biobank
1-2 Spectrum Way
Adswood
Stockport
Cheshire
SK3 0SA

Email: ukbiobank@ukbiobank.ac.uk

We shall reply to your letter promptly in writing, unless you enclose your telephone number and wish to discuss your concerns with us.

Appendix 3: UK Biobank consent

Consent Form for the imaging assessment: UK Biobank

Assessment centre number: [INSERT CENTRE NUMBER]

Participant identifier: [INSERT PARTICIPANT IDENTIFIER]

I have read and understand the Information Leaflet, and have had the opportunity to ask questions.	I agree
I understand that my participation is voluntary and that I am free to withdraw at any time during the imaging visit without giving any reason and that this will not affect my on-going relationship with UK Biobank.	I agree
I understand that these scans are for research purposes only. They will not be routinely examined by medical staff, and should not be regarded as part of a 'health-check'.	I agree
I give permission for long-term storage and use of my imaging scans, other data and biological samples collected for health-related research purposes (even after my incapacity or death) and relinquish all rights to these samples, which I am donating to UK Biobank.	I agree
I give permission for UK Biobank to inform me and my General Practitioner (GP) if a potentially serious abnormality is found on a scan (i.e. one that indicates the possibility of a condition which, if confirmed, carries a real prospect of significantly threatening life span, or of having a substantial impact on major body functions or quality of life).	I agree
I understand that, if UK Biobank does not contact me and my GP about a potentially serious abnormality, this does not imply that no abnormality exists, but simply that no such abnormality was noticed by the staff taking the scans.	I agree
I understand that none of my imaging scans will be given to me at the end of the visit.	I agree
I agree to take part in the imaging assessment for UK Biobank on this basis.	I agree

[INSERT PARTICIPANT NAME]	[INSERT DATE]	[INSERT PARTICIPANT SIGNATURE]
Volunteer name	**Date**	**Signature**

[INSERT STAFF MEMBER NAME]	[INSERT DATE]	
Staff member name	**Date**	

For further information, please call 0800-0-276-276 or go to www.ukbiobank.ac.uk

Version January 2014

Appendix 4: Physical and mental health comorbidity lists

Physical comorbidities

Cardiovascular diseases	**Hypertension**	Hypertension
		Essential hypertension
		Gestational hypertension/ pre-eclampsia
	Previous heart attack/myocardial infarction	Heart attack/myocardial infarction
	Heart failure/pulmonary oedema	Heart failure/pulmonary oedema
	Atrial fibrillation	Atrial fibrillation
	Stroke or transient ischaemic attack	Stroke
		Subarachnoid haemorrhage
		Brain haemorrhage
		Ischaemic stroke
		Transient ischaemic attack
	Peripheral vascular disease	Peripheral vascular disease
		Leg claudication/intermittent claudication
		Arterial embolism
		Aortic aneurysm
		Aortic aneurysm rupture
		Aortic dissection
	Venous thromboembolic disease	Venous thromboembolic disease
		Pulmonary embolism +/- deep venous thrombosis
		Deep venous thrombosis
	High cholesterol	High cholesterol
Respiratory diseases	**Asthma**	Asthma
	Chronic obstructive airways disease/COPD	Chronic obstructive airways disease/COPD
	Chronic sinusitis	Chronic sinusitis
Gastrointestinal/ abdominal diseases	**Irritable bowel syndrome**	Irritable bowel syndrome
	Inflammatory bowel disease	Inflammatory bowel disease
		Crohn's disease

		Ulcerative colitis
	Diverticular disease/diverticulitis	Diverticular disease/diverticulitis
	Cirrhosis/liver failure including alcohol liver disease/alcohol cirrhosis	Liver failure/cirrhosis
		Primary biliary cirrhosis
		Alcoholic liver disease/alcoholic cirrhosis
Renal failure		Renal/kidney failure
		Renal failure requiring dialysis
		Renal failure not requiring dialysis
Endocrine disorders	**Diabetes**	Diabetes
		Gestational diabetes
		Type 1 diabetes
		Type 2 diabetes
		Diabetes insipidus
	Thyroid problem	Thyroid problem (not cancer)
		Hyperthyroidism/thyrotoxicosis
		Hypothyroidism/myxoedema
		Thyroid radioablation therapy
		Thyroiditis
		Grave's disease
		Thyroid goitre
		Parathyroid gland problem (not cancer)
Neurology/eye diseases	**Multiple sclerosis**	Multiple sclerosis
	Epilepsy	Epilepsy
	Migraine	Migraine
	Glaucoma	Glaucoma
	Cataract	Cataract
Musculoskeletal diseases	**Rheumatoid arthritis or psoriatic arthritis**	Rheumatoid arthritis
		Psoriatic arthropathy
	Osteoarthritis	Osteoarthritis
	Gout	Gout
Any cancer	**Ear/nose/throat cancer**	Cancer of lip/mouth/pharynx/oral cavity
		Salivary gland cancer
		Parotid gland cancer

	Other salivary gland cancer
	Lip cancer
	Tongue cancer
	Gum cancer
	Mouth cancer
	Tonsil cancer
	Oropharynx/oropharyngeal cancer
	Nasal cavity cancer
	Sinus cancer
Gastrointestinal cancer	Oesophageal cancer
	Stomach cancer
	Small intestine/small bowel cancer
	Large bowel cancer/colorectal cancer
	Colon cancer/sigmoid cancer
	Appendix cancer
	Rectal cancer
	Anal cancer
	Liver/hepatocellular cancer
	Gallbladder/bile duct cancer
	Pancreas cancer
	Malignant insulinoma
Neurological system cancer	Peripheral nerve/autonomic nerve cancer
	Eye and/or adnexal cancer
	Retinoblastoma
	Meningeal cancer/malignant meningioma
	Brain cancer/primary malignant brain tumour
	Spinal cord or cranial nerve cancer
Urinary tract cancer	Kidney/renal cell cancer
	Bladder cancer
	Other cancer of urinary tract
Breast cancer	Breast cancer
Genital tract cancer	Female genital tract cancer

		Ovarian cancer
		Uterine/endometrial cancer
		Cervical cancer
		Cin/pre-cancer cells cervix
		Vaginal cancer
		Vulval cancer
		Fallopian tube cancer
		Male genital tract cancer
		Prostate cancer
		Testicular cancer
		Penis cancer
Haematological malignancy		Lymphoma
		Hodgkins lymphoma/hodgkins disease
		Non-hodgkins lymphoma
		Leukaemia
		Chronic lymphocytic
		Chronic myeloid
		Acute myeloid leukaemia
		Multiple myeloma
		Myelofibrosis or myelodysplasia
		Other haematological malignancy
Skin cancer		Skin cancer
	Malignant melanoma	Malignant melanoma
	Non-melanoma skin cancer	Non-melanoma skin cancer
		Basal cell carcinoma
		Rodent ulcer
		Squamous cell carcinoma
Other cancer		Primary bone cancer
		Mesothelioma
		Thyroid cancer
		Parathyroid cancer
		Adrenal cancer
		Sarcoma/fibrosarcoma
		Malignant lymph node, unspecified
		Metastatic cancer (unknown

	primary)
	Bone metastases/bony secondaries
	Kaposis sarcoma
Respiratory/intrathoracic cancer	Respiratory/intrathoracic cancer
	Lung cancer
	Small cell lung cancer
	Non-small cell lung cancer
	Larynx/throat cancer
	Ear cancer
	Trachea cancer
	Thymus cancer/malignant thymoma
	Heart/mediastinum cancer

Abbreviation: COPD, chronic obstructive pulmonary disease

Mental health comorbidities

Depression	Depression
	Post-natal depression
Anxiety/panic attacks	Anxiety/panic attacks
Schizophrenia or mania/bipolar disorder/manic depression	Schizophrenia
	Mania/bipolar disorder/manic depression
Alcohol dependency	Alcohol dependency
Anorexia/bulimia/other eating disorder	Anorexia/bulimia/other eating disorder

Appendix 5: Search strategies

Search strategy: MEDLINE

1 exp Psoriasis/
2 psoriasis$.ti,ab.
3 psoriatic$.ti,ab.
4 1 or 2 or 3
5 exp Biological Products/
6 biologic$ product$.ti,ab.
7 exp Biological Therapy/
8 biologic$ therap$.ti,ab.
9 biologic$ treatment$.ti,ab.
10 biologic$ medicine$.ti,ab.
11 biologic$ medication$.ti,ab.
12 biologic$ agent$.ti,ab.
13 tumo?r necrosis factor inhibitor$.ti,ab.
14 tumo?r necrosis factor alpha inhibitor$.ti,ab.
15 TNF inhibitor$.ti,ab.
16 TNF blocker$.ti,ab.
17 TNFi$.ti,ab.
18 TNF-alpha inhibitor$.ti,ab.
19 anti-TNF treatment$.ti,ab.
20 anti-TNF therap$.ti,ab.
21 anti-TNF alpha therap$.ti,ab.
22 anti-TNF alpha treatment$.ti,ab.
23 Anti-TNF agent$.ti,ab.
24 Anti-TNF-alpha agent$.ti,ab.
25 adalimumab.ti,ab.
26 Humira.ti,ab.
27 etanercept.ti,ab.
28 Enbrel.ti,ab.
29 infliximab.ti,ab.
30 Remicade.ti,ab.
31 exp Antibodies, Monoclonal/
32 monoclonal antibod$.ti,ab.
33 ustekinumab.ti,ab.
34 Stelara.ti,ab.
35 secukinumab.ti,ab.
36 Cosentyx.ti,ab.
37 ixekizumab.ti,ab.
38 Taltz.ti,ab.

39 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38

40 "randomized controlled trial".pt.

41 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.

42 (retraction of publication or retracted publication).pt.

43 or/40-42

44 (animals not humans).sh.

45 ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.

46 (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.

47 43 not (44 or 45 or 46)

48 4 and 39 and 47

Search strategy: Embase

1 exp psoriasis/
2 psoriasis$.ti,ab.
3 psoriatic$.ti,ab.
4 1 or 2 or 3
5 exp biological product/
6 biologic$ product$.ti,ab.
7 exp biological therapy/
8 biologic$ therap$.ti,ab.
9 biologic$ treatment$.ti,ab.
10 biologic$ medicine$.ti,ab.
11 biologic$ medication$.ti,ab.
12 biologic$ agent$.ti,ab.
13 exp tumor necrosis factor inhibitor/
14 Tumo?r necrosis factor inhibitor$.ti,ab.
15 exp tumor necrosis factor alpha inhibitor/
16 Tumo?r necrosis factor alpha inhibitor$.ti,ab.
17 TNF inhibitor$.ti,ab.
18 TNF blocker$.ti,ab.
19 TNFi$.ti,ab.
20 TNF-alpha inhibitor$.ti,ab.
21 anti-TNF treatment$.ti,ab.
22 anti-TNF therap$.ti,ab.
23 anti-TNF alpha therap$.ti,ab.
24 anti-TNF alpha treatment$.ti,ab.
25 Anti-TNF agent$.ti,ab.
26 Anti-TNF-alpha agent$.ti,ab.
27 exp adalimumab/
28 adalimumab.ti,ab.
29 Humira.ti,ab.
30 exp etanercept/
31 etanercept.ti,ab.
32 Enbrel.ti,ab.
33 exp infliximab/
34 infliximab.ti,ab.
35 Remicade.ti,ab.
36 exp monoclonal antibody/
37 monoclonal antibod$.mp.
38 exp ustekinumab/
39 ustekinumab.ti,ab.
40 Stelara.ti,ab.

41 exp secukinumab/

42 secukinumab.ti,ab.

43 Cosentyx.ti,ab.

44 exp ixekizumab/

45 ixekizumab.ti,ab.

46 Taltz.ti,ab.

47 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46

48 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.

49 RETRACTED ARTICLE/

50 48 or 49

51 (animal$ not human$).sh,hw.

52 (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/

53 (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/

54 50 not (51 or 52 or 53)

55 4 and 47 and 54

Search strategy: EBM Reviews - ACP Journal Club, EBM Reviews - Cochrane Central Register of Controlled Trials, EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Cochrane Methodology Register, EBM Reviews - Database of Abstracts of Reviews of Effects, EBM Reviews - Health Technology Assessment, EBM Reviews - NHS Economic Evaluation Database

1 psoriasis$.ti,ab.
2 Psoriatic$.ti,ab.
3 1 or 2
4 Biologic$ product$.ti,ab.
5 Biologic$ therap$.ti,ab.
6 Biologic$ treatment$.ti,ab.
7 Biologic$ medicine$.ti,ab.
8 Biologic$ medication$.ti,ab.
9 Biologic$ agent$.ti,ab.
10 Tumo?r necrosis factor inhibitor$.ti,ab.
11 Tumo?r necrosis factor alpha inhibitor$.ti,ab.
12 TNF inhibitor$.ti,ab.
13 TNFi$.ti,ab.
14 TNF-alpha inhibitor$.ti,ab.
15 TNF blocker$.ti,ab.
16 anti-TNF treatment$.ti,ab.
17 anti-TNF therap$.ti,ab.
18 anti-TNF alpha therap$.ti,ab.
19 anti-TNF alpha treatment$.ti,ab.
20 Anti-TNF agent$.ti,ab.
21 Anti-TNF-alpha agent$.ti,ab.
22 adalimumab.ti,ab.
23 Humira.ti,ab.
24 Etanercept.ti,ab.
25 Enbrel.ti,ab.
26 Infliximab.ti,ab.
27 Remicade.ti,ab.
28 monoclonal antibod$.ti,ab.
29 ustekinumab.ti,ab.
30 Stelara.ti,ab.
31 secukinumab.ti,ab.
32 Cosentyx.ti,ab.
33 ixekizumab.ti,ab.
34 Taltz.ti,ab.

35 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34

36 3 and 35

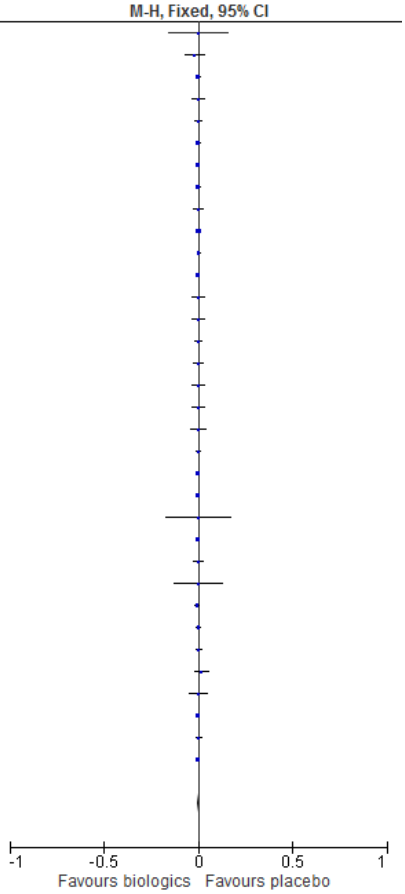
37 remove duplicates from 36

Appendix 6: Figures of Mantel-Haenszel risk differences of major adverse cardiovascular events and funnel plots for the detection of publication bias

Figure Mantel-Haenszel risk difference of major adverse cardiovascular events and a funnel plot for the detection of publication bias in patients treated with biologic therapies versus placebo

Study or Subgroup	Biologics Events	Biologics Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Chaudhari et.al., 2001	0	11	0	11	0.2%	0.00 [-0.16, 0.16]	2001
Gottlieb et.at., 2003	0	57	1	55	0.9%	-0.02 [-0.07, 0.03]	2003
Leonardi et.al., 2003	0	486	0	166	3.9%	0.00 [-0.01, 0.01]	2003
Gottlieb et.al., 2004	0	99	0	51	1.0%	0.00 [-0.03, 0.03]	2004
Reich et.al., 2005	0	298	0	76	1.9%	0.00 [-0.02, 0.02]	2005
Papp et.al., 2005	0	390	0	193	4.0%	0.00 [-0.01, 0.01]	2005
Tyring et.al., 2006	0	312	0	306	4.8%	0.00 [-0.01, 0.01]	2006
Menter et.al., 2007	0	314	0	207	3.9%	0.00 [-0.01, 0.01]	2007
Saurat et.al., 2008	0	107	0	53	1.1%	0.00 [-0.03, 0.03]	2008
Papp et.al., 2008	1	820	0	410	8.5%	0.00 [-0.00, 0.01]	2008
Leonardi et.al. 2008	1	510	0	255	5.3%	0.00 [-0.01, 0.01]	2008
Menter et.al., 2008	0	814	0	398	8.3%	0.00 [-0.00, 0.00]	2008
Van de Kerkhof et.al., 2008	0	96	0	46	1.0%	0.00 [-0.03, 0.03]	2008
Tsai et.al., 2011	0	61	0	60	0.9%	0.00 [-0.03, 0.03]	2011
Strober et.al, 2011	0	139	0	72	1.5%	0.00 [-0.02, 0.02]	2011
Gottlieb et.al., 2011	0	141	0	68	1.4%	0.00 [-0.02, 0.02]	2011
Bagel et.al., 2012	0	59	0	62	0.9%	0.00 [-0.03, 0.03]	2012
Yang et.al., 2012	0	84	0	45	0.9%	0.00 [-0.03, 0.03]	2012
Igarashi et.al., 2012	0	126	0	32	0.8%	0.00 [-0.04, 0.04]	2012
Zhu et.al., 2013	0	160	0	161	2.5%	0.00 [-0.01, 0.01]	2013
Langley et.al., 2014 (ERASURE)	0	490	0	247	5.1%	0.00 [-0.01, 0.01]	2014
Langley et.al., 2014 (FIXTURE)	0	976	0	327	7.6%	0.00 [-0.00, 0.00]	2014
Maari et.al., 2014	0	10	0	10	0.2%	0.00 [-0.17, 0.17]	2014
Lebwohl et.al., 2015 (AMAGINE 2)	0	300	0	309	4.7%	0.00 [-0.01, 0.01]	2015
Paul et.al., 2015	0	121	0	61	1.3%	0.00 [-0.02, 0.02]	2015
NCT01276847, 2015	0	30	0	10	0.2%	0.00 [-0.13, 0.13]	2015
Griffiths et.al., 2015 (UNCOVER-3)	0	766	1	193	4.8%	-0.01 [-0.02, 0.01]	2015
Griffiths et.al., 2015 (UNCOVER-2)	1	707	0	167	4.2%	0.00 [-0.01, 0.01]	2015
Bachelez et.al., 2015	1	335	0	107	2.5%	0.00 [-0.01, 0.02]	2015
Blauvelt et.al., 2015	2	118	0	59	1.2%	0.02 [-0.02, 0.05]	2015
Gordon et.al., 2015	0	43	0	42	0.7%	0.00 [-0.04, 0.04]	2015
Lebwohl et.al., 2015 (AMAGINE 3)	0	313	0	315	4.9%	0.00 [-0.01, 0.01]	2015
NCT01646073, 2015	1	338	0	87	2.2%	0.00 [-0.01, 0.02]	2015
Gordon et.al., 2016 (UNCOVER-1)	0	433	0	431	6.7%	0.00 [-0.00, 0.00]	2016
Total (95% CI)		**10064**		**5092**	**100.0%**	**0.00 [-0.00, 0.00]**	
Total events	7		2				

Heterogeneity: Chi² = 2.96, df = 33 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)



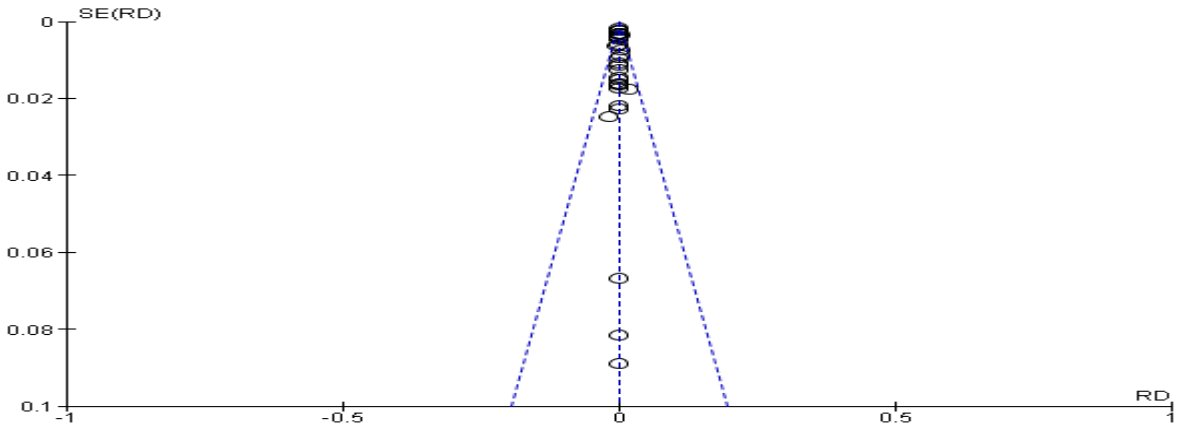
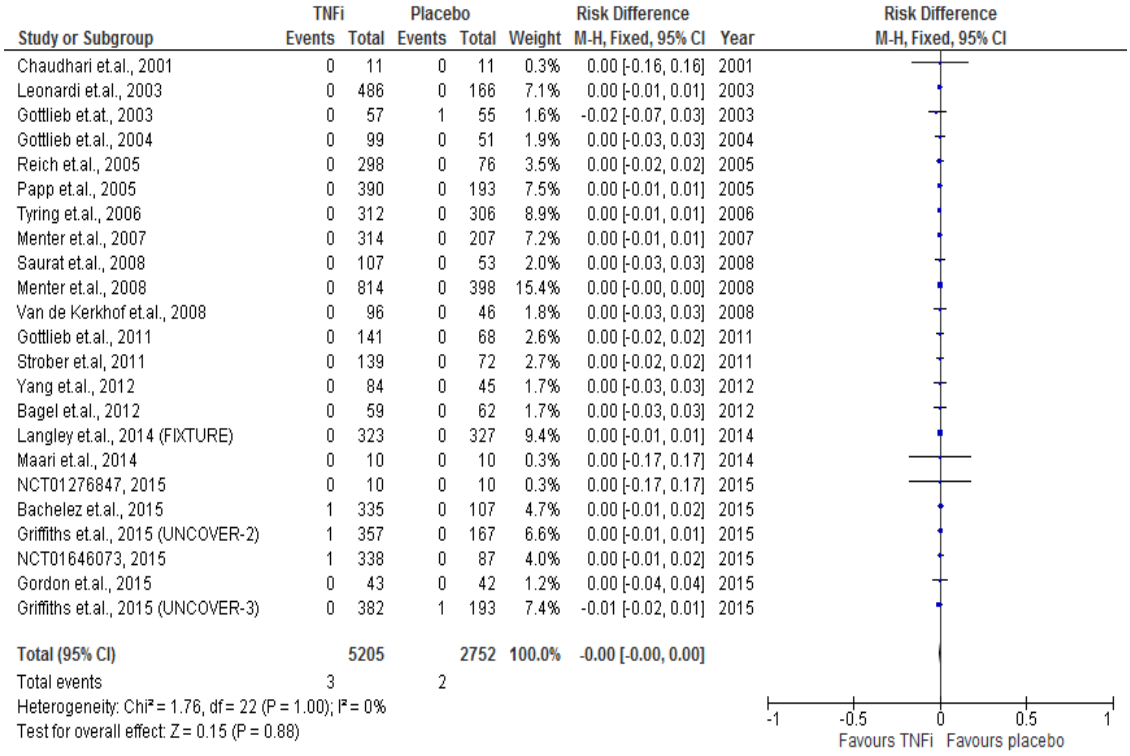


Figure Mantel-Haenszel risk difference of major adverse cardiovascular events and a funnel plot for the detection of publication bias in patients treated with tumour necrosis factor-alpha inhibitors versus placebo



Study or Subgroup	TNFi Events	TNFi Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Chaudhari et.al., 2001	0	11	0	11	0.3%	0.00 [-0.16, 0.16]	2001
Leonardi et.al., 2003	0	486	0	166	7.1%	0.00 [-0.01, 0.01]	2003
Gottlieb et.at., 2003	0	57	1	55	1.6%	-0.02 [-0.07, 0.03]	2003
Gottlieb et.al., 2004	0	99	0	51	1.9%	0.00 [-0.03, 0.03]	2004
Reich et.al., 2005	0	298	0	76	3.5%	0.00 [-0.02, 0.02]	2005
Papp et.al., 2005	0	390	0	193	7.5%	0.00 [-0.01, 0.01]	2005
Tyring et.al., 2006	0	312	0	306	8.9%	0.00 [-0.01, 0.01]	2006
Menter et.al., 2007	0	314	0	207	7.2%	0.00 [-0.01, 0.01]	2007
Saurat et.al., 2008	0	107	0	53	2.0%	0.00 [-0.03, 0.03]	2008
Menter et.al., 2008	0	814	0	398	15.4%	0.00 [-0.00, 0.00]	2008
Van de Kerkhof et.al., 2008	0	96	0	46	1.8%	0.00 [-0.03, 0.03]	2008
Gottlieb et.al., 2011	0	141	0	68	2.6%	0.00 [-0.02, 0.02]	2011
Strober et.al, 2011	0	139	0	72	2.7%	0.00 [-0.02, 0.02]	2011
Yang et.al., 2012	0	84	0	45	1.7%	0.00 [-0.03, 0.03]	2012
Bagel et.al., 2012	0	59	0	62	1.7%	0.00 [-0.03, 0.03]	2012
Langley et.al., 2014 (FIXTURE)	0	323	0	327	9.4%	0.00 [-0.01, 0.01]	2014
Maari et.al., 2014	0	10	0	10	0.3%	0.00 [-0.17, 0.17]	2014
NCT01276847, 2015	0	10	0	10	0.3%	0.00 [-0.17, 0.17]	2015
Bachelez et.al., 2015	1	335	0	107	4.7%	0.00 [-0.01, 0.02]	2015
Griffiths et.al., 2015 (UNCOVER-2)	1	357	0	167	6.6%	0.00 [-0.01, 0.01]	2015
NCT01646073, 2015	1	338	0	87	4.0%	0.00 [-0.01, 0.02]	2015
Gordon et.al., 2015	0	43	0	42	1.2%	0.00 [-0.04, 0.04]	2015
Griffiths et.al., 2015 (UNCOVER-3)	0	382	1	193	7.4%	-0.01 [-0.02, 0.01]	2015
Total (95% CI)		**5205**		**2752**	**100.0%**	**-0.00 [-0.00, 0.00]**	
Total events	3		2				

Heterogeneity: Chi² = 1.76, df = 22 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)

Risk Difference M-H, Fixed, 95% CI

-1 -0.5 0 0.5 1
Favours TNFi Favours placebo

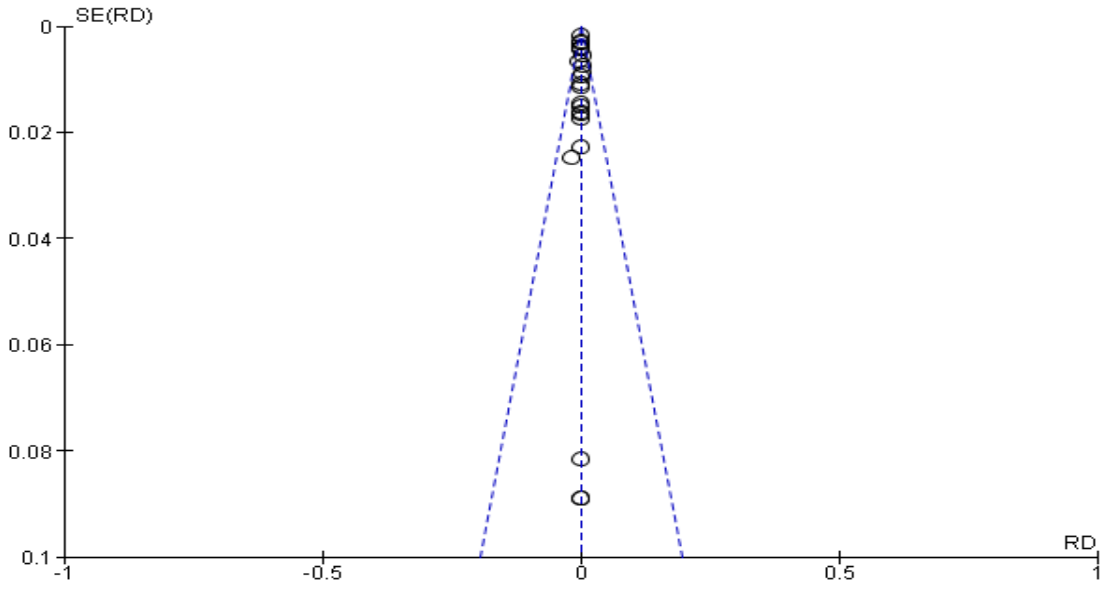
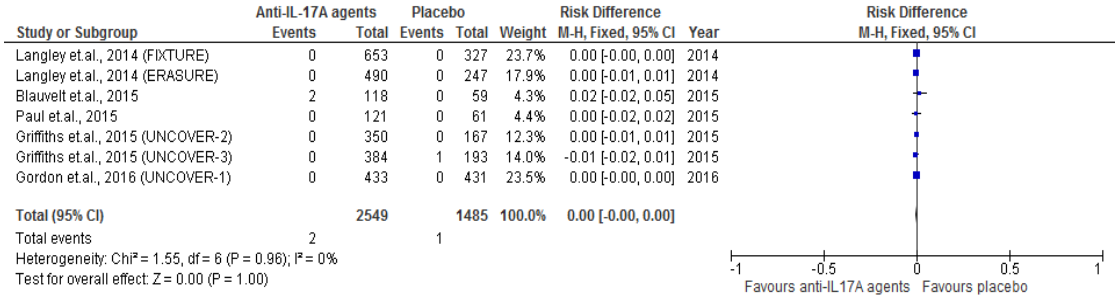


Figure Mantel-Haenszel risk difference of major adverse cardiovascular events and a funnel plot for the detection of publication bias in patients treated with anti-interleukin-17A agents versus placebo



Study or Subgroup	Anti-IL-17A agents Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Langley et.al., 2014 (FIXTURE)	0	653	0	327	23.7%	0.00 [-0.00, 0.00]	2014
Langley et.al., 2014 (ERASURE)	0	490	0	247	17.9%	0.00 [-0.01, 0.01]	2014
Blauvelt et.al., 2015	2	118	0	59	4.3%	0.02 [-0.02, 0.05]	2015
Paul et.al., 2015	0	121	0	61	4.4%	0.00 [-0.02, 0.02]	2015
Griffiths et.al., 2015 (UNCOVER-2)	0	350	0	167	12.3%	0.00 [-0.01, 0.01]	2015
Griffiths et.al., 2015 (UNCOVER-3)	0	384	1	193	14.0%	-0.01 [-0.02, 0.01]	2015
Gordon et.al., 2016 (UNCOVER-1)	0	433	0	431	23.5%	0.00 [-0.00, 0.00]	2016
Total (95% CI)		**2549**		**1485**	**100.0%**	**0.00 [-0.00, 0.00]**	
Total events	2		1				

Heterogeneity: Chi² = 1.55, df = 6 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

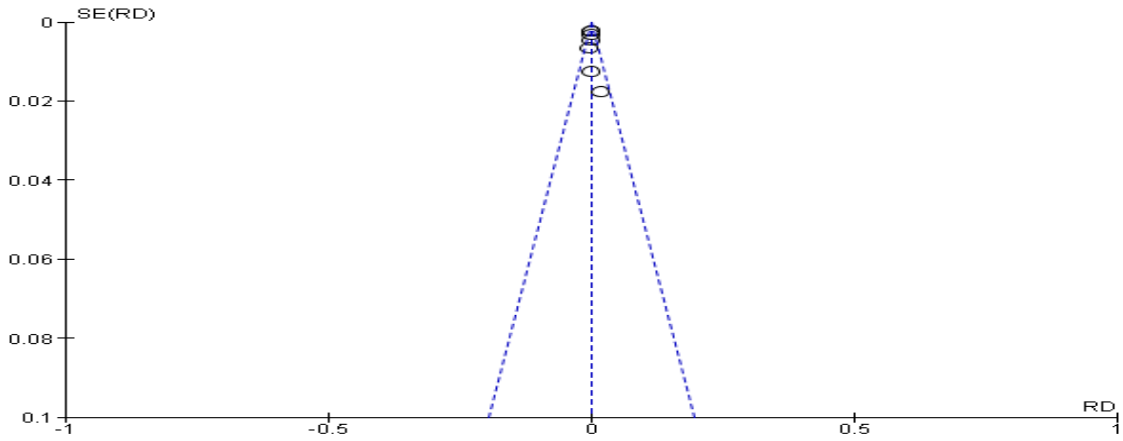
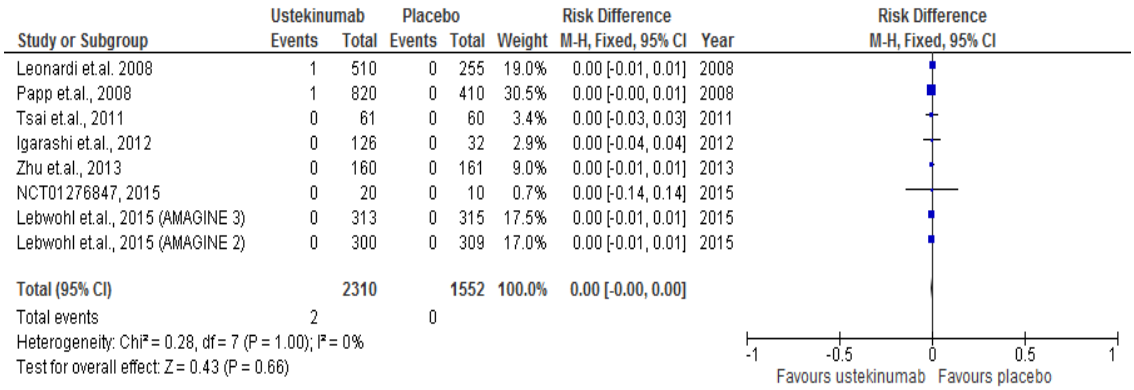


Figure Mantel-Haenszel risk difference of major adverse cardiovascular events and a funnel plot for the detection of publication bias in patients treated with ustekinumab versus placebo



Study or Subgroup	Ustekinumab Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Leonardi et.al. 2008	1	510	0	255	19.0%	0.00 [-0.01, 0.01]	2008
Papp et.al., 2008	1	820	0	410	30.5%	0.00 [-0.00, 0.01]	2008
Tsai et.al., 2011	0	61	0	60	3.4%	0.00 [-0.03, 0.03]	2011
Igarashi et.al., 2012	0	126	0	32	2.9%	0.00 [-0.04, 0.04]	2012
Zhu et.al., 2013	0	160	0	161	9.0%	0.00 [-0.01, 0.01]	2013
NCT01276847, 2015	0	20	0	10	0.7%	0.00 [-0.14, 0.14]	2015
Lebwohl et.al., 2015 (AMAGINE 3)	0	313	0	315	17.5%	0.00 [-0.01, 0.01]	2015
Lebwohl et.al., 2015 (AMAGINE 2)	0	300	0	309	17.0%	0.00 [-0.01, 0.01]	2015
Total (95% CI)		**2310**		**1552**	**100.0%**	**0.00 [-0.00, 0.00]**	
Total events	2		0				

Heterogeneity: Chi² = 0.28, df = 7 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.66)

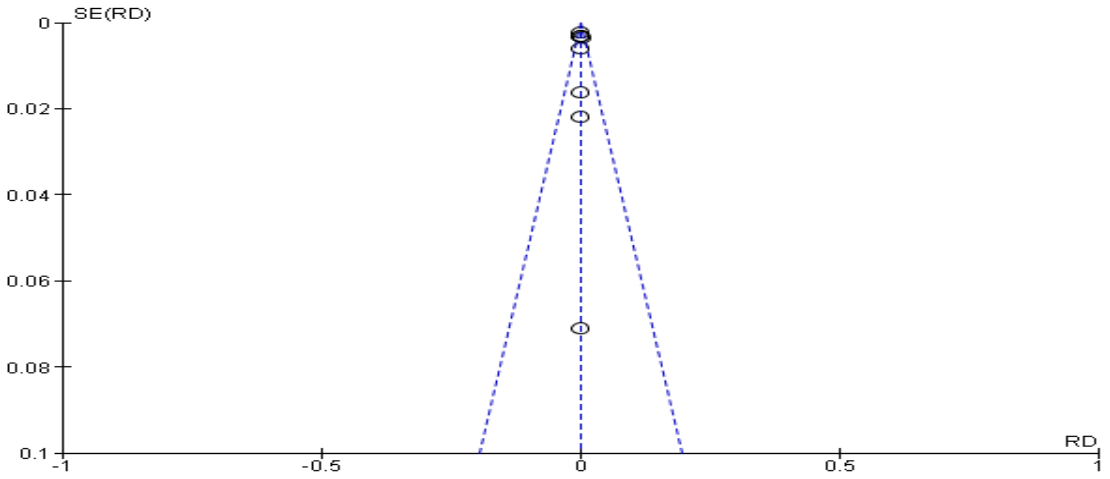
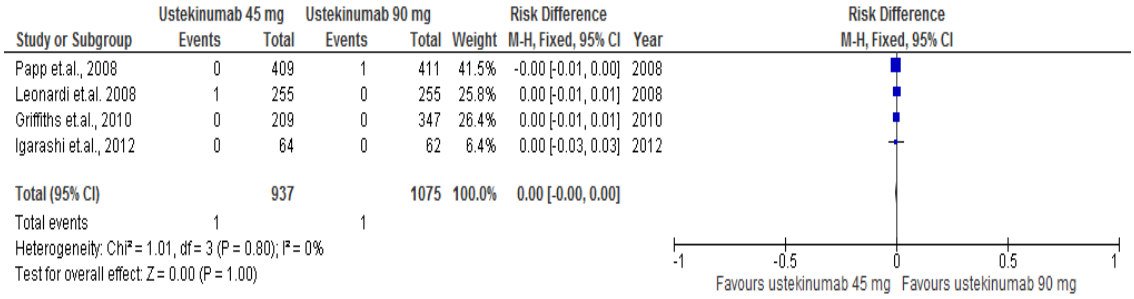


Figure Mantel-Haenszel risk difference of major adverse cardiovascular events and a funnel plot for the detection of publication bias in patients treated with ustekinumab 45 mg versus 90 mg



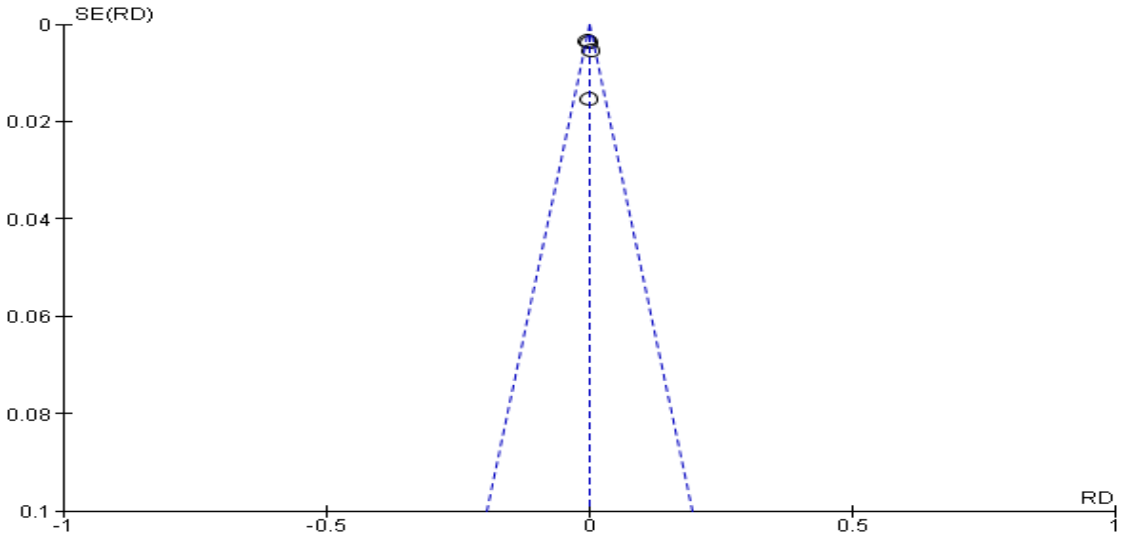
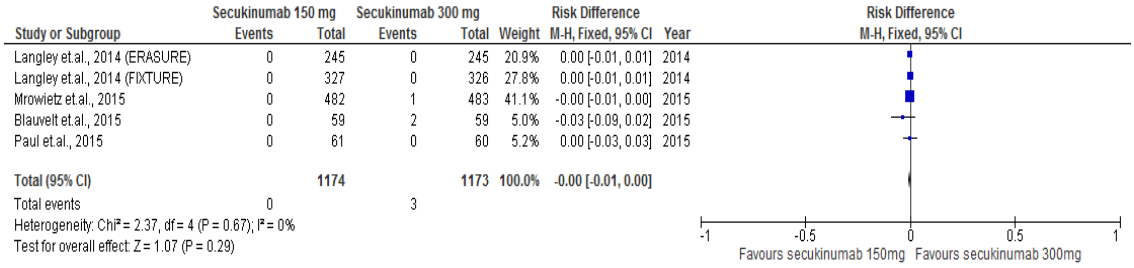
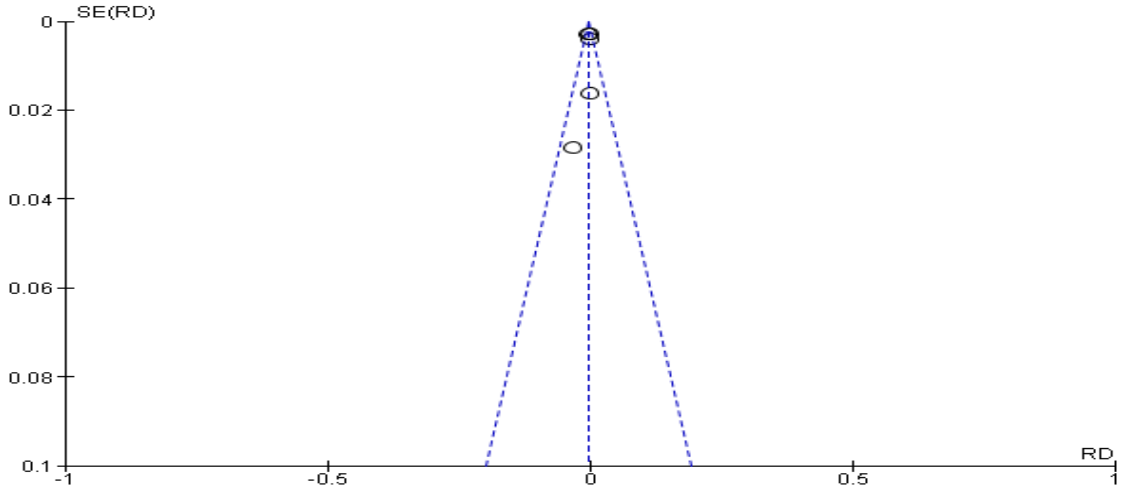


Figure Mantel-Haenszel risk difference of major adverse cardiovascular events and a funnel plot for the detection of publication bias in patients treated with secukinumab 150 mg versus 300 mg





Appendix 7: BADBIR ethical approval by the North West NHS multicentre research ethics committee

NHS

North West Research Ethics Committee

NHS North West
Room 155 - Gateway House
Piccadilly South
Manchester
M60 7LP

Telephone: 0161 237 2152
Facsimile: 0161 237 2583

14 March 2007

Professor C E M Griffiths
Professor of Dermatology
The University of Manchester
Dermatology Centre
Hope Hospital
Stott Lane
SALFORD M6 8HD

RECEIVED
16 MAR 2007

Dear Professor Griffiths

Full title of study: **British Association of Dermatologists Biological Interventions Register**

REC reference number: **07/MRE08/9**

Thank you for your letter of 05 March 2007, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair (Dr Donal Manning) and Mr James Bruce (Consultant Surgeon).

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation [as revised].

Ethical review of research sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the research site(s) taking part in this study. The favourable opinion does not therefore apply to any site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at sites requiring SSA.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

The Central Office for Research Ethics Committees is Responsible for the operational management of Multi-Centre Research Ethics Committees

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application	5.2	18 December 2006
Investigator CV - for Professor C E M Griffiths		19 December 2006
Protocol	10	05 December 2006
Covering Letter		19 December 2006
Peer Review - from Professor Nils Feltenius, Director of ARTIS registry, Karolinska University Hospital Solna - August 2006		
Statistician Comments - Letter from Dr Chris Roberts, Senior Lecturer in Medical Statistics, The University of Manchester		25 October 2006
Questionnaire: Patient baseline questionnaire	4	08 December 2006
Questionnaire: Consultant 6-monthly follow-up questionnaire	4	08 December 2006
Questionnaire: Consultant baseline questionnaire	4	08 December 2006
Questionnaire: Patient 6-monthly follow-up questionnaire	4	08 December 2006
Questionnaire: Psoriasis Area and Severity Index - PASI (validated)		
Questionnaire: Dermatology Life Quality Index - DLQI (validated)		
Questionnaire: CAGE Questionnaire (validated)		
Questionnaire: Generic Health Utility Index - Patient Baseline EuroQol (validated)		
Questionnaire: Health Assessment Questionnaire (HAQ) - rheumatoid arthritis only) (validated)		
Questionnaire: BAD Biological Interventions Register - Patient 6-monthly diary	4	08 December 2006
Questionnaire: Serious Adverse Event Further Information Form: Serious Infections (excluding TB)	1	08 December 2006
Questionnaire: Serious Adverse Event Further Information Form: Lymphoproliferative tumours	1	08 December 2006
Questionnaire: Serious Adverse Event Further Information Form: Congestive Heart Failure	1	08 December 2006
Questionnaire: Serious Adverse Event Further Information Form: Central demyelinating disease	1	08 December 2006
Questionnaire: Serious Adverse Event Further Information Form: Aplastic anaemia / pancytopaenia	1	08 December 2006
Questionnaire: Control Patient follow-up questionnaire	4	08 December 2006
Questionnaire: Pregnancy Outcome Questionnaire	1	08 December 2006
Questionnaire: Serious Adverse Event Further Information Form: Tuberculosis	1	08 December 2006
Participant Information Sheet	1	08 December 2006
Participant Information Sheet	2	
Participant Consent Form	1	08 December 2006
Response to Request for Further Information - From Professor EM Griffiths		05 March 2007
Patient Follow-up Flow Chart		
Website content		
Letter from funder - British Association of Dermatologists		07 December 2006

R&D approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final approval from the R&D office for the relevant NHS care organisation.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

07/MRE08/9	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

p.p. **Dr Donal Manning**
Chair

Email: northwest.mrec@northwest.nhs.uk

Enclosures: Standard approval conditions

Copies to: -

Dr K D Watson
ARC Epidemiology Unit
The University of Manchester
Stopford Building
Oxford Road
MANCHESTER
M13 9PT

R&D Department for NHS care organisation at lead site: -

Dr K Shaw
Head of the University Research Office
University of Manchester
Christie Building
Oxford Road
MANCHESTER
M13 9PL

Appendix 8: Patient information sheet for patients over 16 years of age

To be printed on hospital headed paper

PATIENT INFORMATION SHEET

Title of Project:
British Association of Dermatologists Biologic Interventions Register (BADBIR)

What is the purpose of the study?

The purpose of the research study is to assess whether new biologic or immunomodulator treatments (such as Benepali, Cosentyx, Taltz, Humira, Stelara) used in the treatment of psoriasis have a greater risk of serious side effects or long term health problems than established treatments such as ciclosporin, methotrexate and PUVA. As psoriasis is a long term condition requiring lifelong treatment it is important to establish how these drugs compare to the other treatment options available in terms of safety when used long-term (for a period of many years).

The biologic drugs and immunomodulators have been carefully tested in clinical trials before being approved for use. However, as clinical trials are run for a relatively short period of time (on average up to a year), have limited numbers of participants compared with those which will be ultimately treated with the drug and may exclude patients with additional diseases (co-morbidities), it may mean that the picture might not be complete in terms of long-term use.

In contrast, BADBIR will collect information (data) on patients treated with biologics and immunomodulators attending regular dermatology clinics over a long period. Patients who have co-morbidities will also be included therefore the results are likely to be more representative of the "real world" use of these drugs.

The study is designed such that a large group of patients being treated with biologics and immunomodulators are compared to an equally large group of patients treated with established therapies (conventional). The study team will observe how often side effects occur in all three groups of patients.

Rates of untoward medical events will be compared between the groups and the results will then be used to provide patients with a better picture of any increased risk of the new therapies.

The study is being funded by the British Association of Dermatologists (BAD), a society of dermatologists aiming to give the best patient care to individuals with skin diseases. The BAD receive funds from a number of pharmaceutical companies who manufacture the biologic therapies to support this study.

Why have I been chosen and what your contribution means?

You have been chosen to participate as you have been started on a biologic, immunomodulator therapy or one of the established treatments for psoriasis. By participating, you will help us build up the amount of data available for analysis.

Do I have to take part?

You do not have to take part. If you do decide to take part, you can keep this sheet and will be asked to sign a consent form. Your participation will not interfere with the standard of care you receive. By signing the consent form, you would be confirming your willingness to take part.

What are the risks of taking part?

The study will run alongside your routine clinical care at the hospital; it will not influence this process at all. Therefore, there are no foreseeable medical risks associated with participating in this study.

What are the benefits of taking part?

Although there is no clinical benefit gained by participation in the study, the information obtained from this study may result in changes in future treatment of patients with psoriasis and will help patients and doctors make more informed treatment decisions.

Will the research influence the treatment I receive?

The research does not alter the treatment you receive. Your specialist will start and stop treatments as determined by your clinical condition

What will happen if I take part?

Your participation will involve the following:

(i) Agreement to complete the questionnaires and other survey forms about your health. You should note that some of the questions may be of a sensitive or personal nature. You are not compelled to answer all of the questions.

(ii) Agreement with your specialist to provide information of relevance to this study from your hospital medical records to the BADBIR study team at the University of Manchester. This will be information regarding the treatments you are receiving, assessments of your skin, details of any illnesses you have and body measurements including height and weight. Copies of the data collection questionnaires are available on the BADBIR website http://www.badbir.org/

(iii) Agreement for your date of birth and NHS number (and also in Scotland your name) to be shared with national providers of healthcare data (including NHS Digital in England) for the purpose of linking to information held about any hospital admissions you have had, details if you are registered as having cancer or in the event of your death. This will enable these organisations to provide the BADBIR study team with information about these events that may not have been reported via the dermatology team. This will result in a more complete picture of your health experiences and will enable the study to provide more accurate results on the long-term safety of the biologic and immunomodulating drugs. There are different data providers in each area of the UK. A complete and up to date list of the national data providers linked with BADBIR is summarised at the end of this information sheet in appendix 1. This information can also be viewed at www.badbir.org. Please speak to your dermatologist or clinic nurse if you need assistance accessing this website link.

At this stage we do not know how long we will want to collect this information from you and about you. It is likely to be for at least five years. Research data will be stored for 15 years following study end and subsequently securely destroyed.

.

How will my data be processed?

Information will be updated at least annually by the dermatology team and collected via a computer system. Data will be sent using a secure network.

How will your data be kept secure and confidential?

The University of Manchester is responsible for the purpose and manner in which your data are processed. They will ensure that your data are processed fairly and lawfully in accordance with the Data Protection Act 1998. Your personal data will not be shared with other parties beyond the data controllers, providers of healthcare data and approved data processors (any person or organisation that processes your data on behalf of the data controllers) where appropriate contractual agreements are in place with the data controllers.

BADBIR at The University of Manchester has a number of rigorous procedures in place to protect your personal data and keep it secure as follows:

- All BADBIR staff will sign annual confidentiality agreements as part of their employment contracts
- Computer security to block unauthorised access to the computers/systems that hold personal information. Personal identifiable data will be held in an encrypted format at the University of Manchester. Encryption allows information to be stored in an unreadable manner making it accessible to the research team (named by the study's Chief Investigator) only with the use of a University of Manchester username and password. This information is held for the sole purpose of linking to information already stored by national providers of healthcare data e.g. NHS Digital in England. Your identifiable data will not be shared with any other parties beyond this.
- If your data is provided as part of a larger dataset to researchers outside of the BADBIR team, information that could identify you will not be provided

Involvement of Third Parties

A number of pharmaceutical companies who manufacture these biologic and immunomodulating therapies will have access to some study data (not personally identifiable e.g. name postcode, NHS/CHI number) so that they can update records with the international regulatory government agencies responsible for drug safety e.g. US Food and Drug Administration (FDA). Therefore, there is a small possibility that medical information may be sent outside the European Union for analysis. By signing the consent form you are agreeing to this transfer.

Your hospital medical records will state that you are in this Register. By signing the consent form, you are allowing the dermatology team to permit these records to be viewed by the BADBIR team at the University of Manchester or possibly agencies such as the MHRA or authorised members of the Ethics Committee or Hospital. This is for the purpose of checking that the data is correct or checking that the study is being carried out properly.

How do I withdraw from the study if I want to?

You can withdraw at any time from the study after giving your signed consent by contacting your local dermatology research team. You do not need to give a reason and your medical care or legal rights will not be affected.

BADBIR will be most valuable if few people withdraw from it, so potential participants are asked to discuss any concerns they might have with their dermatology team or the BADBIR team. The desired level of withdrawal can be selected from the following three options:

Option 1: No further questionnaires:
You would not answer any further questionnaires about your health, but BADBIR would continue to receive information from the team at the hospital and via the linkage with the national providers of healthcare data.

Option 2: No further participant or hospital contact:
No further information would be received from the hospital but information would still be collected through the linkage with the national providers of healthcare data.

Option 3: Complete withdrawal:
No further information would be collected from the hospital and BADBIR would contact the national providers of healthcare data to remove the link to your record so no further information was received on your health status from the time you withdrew.

Who has reviewed the study?

Before any research study can go ahead, it has to be checked by a research ethics committee and the Health Research Authority (HRA) to make sure that the research is fair and transparent. The study has been reviewed and approved by the North West 7 REC GM Central Research Ethics Committee (Ref: 07/MRE08/9).

Who is organising the study?

The study is being co-ordinated and sponsored by the University of Manchester and the lead researchers, Professor Christopher Griffiths or Dr Kathy McElhone can be contacted if you have any concerns about any aspect of this study (Tel: 0161 306 1894). If they are unable to resolve your concern or you wish to make a complaint regarding the study, please contact the Research Practice Governance Co-ordinator at The University of Manchester on 0161 275 5436.

Where can you see the study results?

Any study results or published reports using the data will be anonymised and it will not be possible to identify you.

Study results will be published in medical journals and a summary version will be available at http://www.badbir.org/. These will also be available to your consultant (Tel: ########## Fax: ######### Email: ################# Postal Address in Letterhead) whom you should contact for further information.

Local contact

Appendix 1 - Summary of Linkage Organisations

A summary of the national providers of healthcare data BADBIR links to is outlined below. In England, Wales and Northern Ireland, the BADBIR study will provide your NHS/HCN number alongside your date of birth to link to your record with the data provider. In Scotland, your name and date of birth will be used alongside your CHI number and date of birth. The data returned to the study from every provider will be pseudonymised using your study ID.

This information is accurate at the time this consent form was approved for use. An up-to-date summary will always be available at www.badbir.org. Please speak to your dermatologist or clinic nurse if you need assistance accessing this website link:

England:

Linkage Type	Data Provider
Cancer Registration Data (Malignancy)	NHS Digital on behalf of Public Health England (PHE)
Civil Registration Data (Mortality)	Sourced from civil registration data and provided by NHS Digital on behalf of the Office for National Statistics
Inpatient Admission	NHS Digital (Hospital Episode Statistics)

Northern Ireland:

Linkage Type	Data Provider
Malignancy	Northern Ireland Cancer Registry (NICR)
Mortality	Health and Social Care Business Services Organisation (BSO)

Scotland:

Linkage Type	Data Provider
Malignancy	National Health Service Central Register (NHSCR)
Mortality	National Health Service Central Register (NHSCR)
Inpatient Admission	National Services Scotland (NSS)

Wales:

Linkage Type	Data Provider
Cancer Registration Data	NHS Digital on behalf of Public Health Wales
Civil Registration Data	Sourced from civil registration data and provided by NHS Digital on behalf of the Office for National Statistics
Inpatient Admission	NHS Wales Informatics Service (Patient Episode Database for Wales)

Appendix 9: Patient consent form for patients over 16 years of age

PATIENT CONSENT FORM

Title of Project: **British Association of Dermatologists Biologic Interventions Register**

Name of Chief Investigator: Professor Christopher Griffiths

		Please initial box
1.	I confirm that I have read and understand the information sheet dated 01/08/2017 (version 5) for the above study and have had the opportunity to ask questions.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason and without my medical care or legal rights being affected.	☐
3.	I understand and agree that my identifiable details (date of birth and health service number, name in Scotland only) may be shared with national providers of healthcare data for the purpose of linking to information held about any hospital admissions I have had, details if am registered as having cancer or, in the event of my death. Details of the organisations linked to are available on the final page of the information sheet and at www.badbir.org	☐
4.	I agree to complete the questionnaires and other survey forms about my health.	☐
5.	I agree that my specialist Dr _____ may provide the researchers with information from my Health Records that is relevant to this Study.	☐
6.	I agree to information, from which I can be identified, being held by the research Team at the University of Manchester together with data collected during the study.	☐
7.	I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University Of Manchester, their representatives/ agents, the regulatory authorities and individuals from the Hospital. I give permission for these individuals to have access to my records which will include identifiable information.	☐
8.	I understand that some data, which will not contain information that could identify me, may be transferred out of the UK	☐

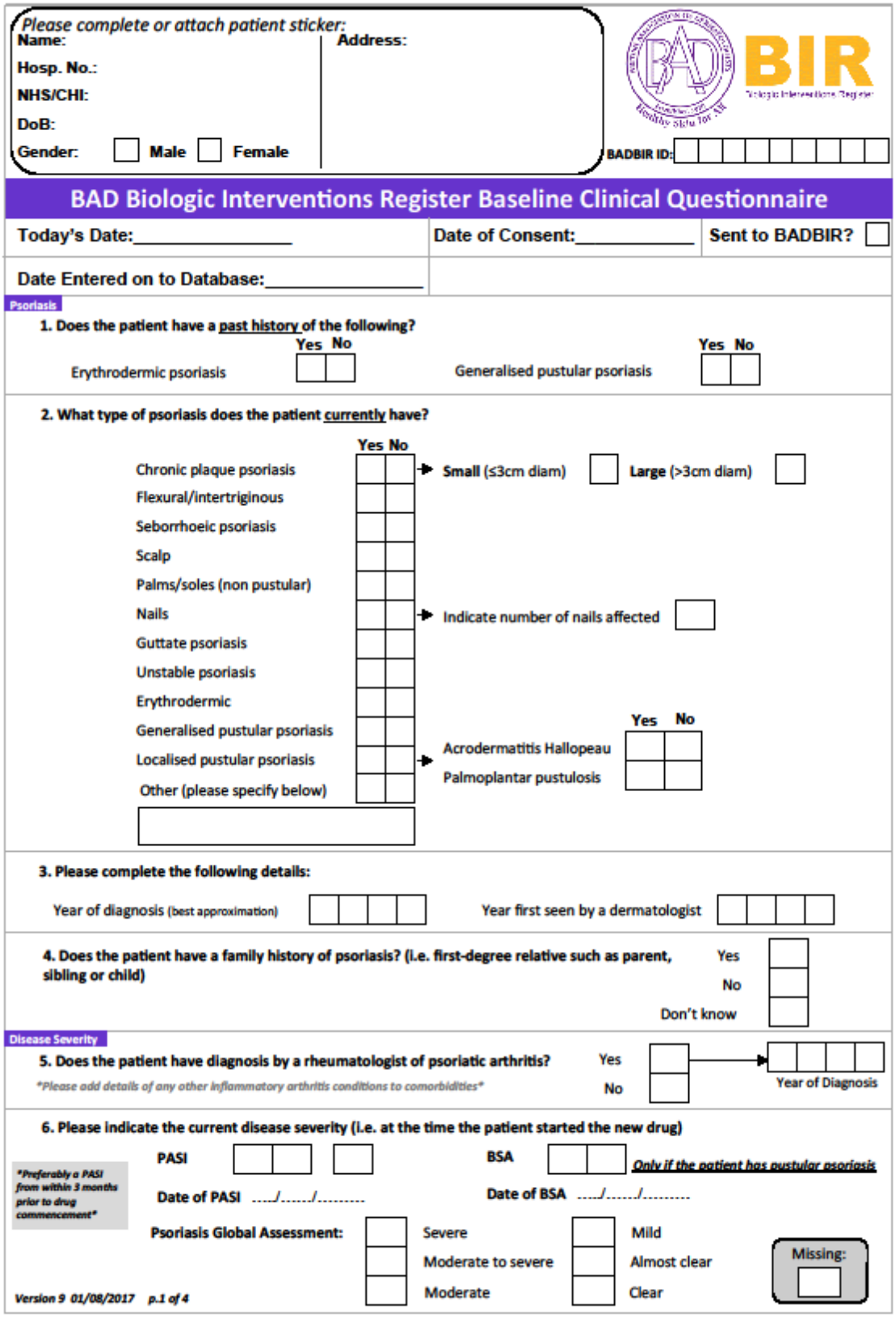
Name of patient	Date	Signature
Name of Person taking consent	Date	Signature

1 copy for patient; 1copy for researcher; 1 copy to be kept with hospital notes

Version 5 01/08/2017

Appendix 10: Baseline questionnaires

Patient clinical questionnaire



Please complete or attach patient sticker:
Name: **Address:**
Hosp. No.:
NHS/CHI:
DoB:
Gender: ☐ **Male** ☐ **Female**

BADBIR ID: ☐☐☐☐☐☐☐☐☐☐

BAD Biologic Interventions Register Baseline Clinical Questionnaire

Today's Date:_____ **Date of Consent:**_____ **Sent to BADBIR?** ☐

Date Entered on to Database:_____

Psoriasis

1. Does the patient have a past history of the following?

	Yes	No		Yes	No
Erythrodermic psoriasis	☐	☐	Generalised pustular psoriasis	☐	☐

2. What type of psoriasis does the patient currently have?

	Yes	No	
Chronic plaque psoriasis	☐	☐	→ **Small** (≤3cm diam) ☐ **Large** (>3cm diam) ☐
Flexural/intertriginous	☐	☐	
Seborrhoeic psoriasis	☐	☐	
Scalp	☐	☐	
Palms/soles (non pustular)	☐	☐	
Nails	☐	☐	→ Indicate number of nails affected ☐
Guttate psoriasis	☐	☐	
Unstable psoriasis	☐	☐	
Erythrodermic	☐	☐	
Generalised pustular psoriasis	☐	☐	
Localised pustular psoriasis	☐	☐	→ Acrodermatitis Hallopeau / Palmoplantar pustulosis: Yes ☐ No ☐
Other (please specify below)	☐	☐	

☐

3. Please complete the following details:

Year of diagnosis (best approximation) ☐☐☐☐ Year first seen by a dermatologist ☐☐☐☐

4. Does the patient have a family history of psoriasis? (i.e. first-degree relative such as parent, sibling or child)

Yes ☐
No ☐
Don't know ☐

Disease Severity

5. Does the patient have diagnosis by a rheumatologist of psoriatic arthritis?

Yes ☐ → Year of Diagnosis ☐☐☐☐
No ☐

Please add details of any other inflammatory arthritis conditions to comorbidities

6. Please indicate the current disease severity (i.e. at the time the patient started the new drug)

Preferably a PASI from within 3 months prior to drug commencement

PASI ☐☐ ☐ **BSA** ☐☐ ***Only if the patient has pustular psoriasis***

Date of PASI ..../...../..... **Date of BSA** ..../...../.....

Psoriasis Global Assessment:

☐	Severe	☐	Mild
☐	Moderate to severe	☐	Almost clear
☐	Moderate	☐	Clear

Missing: ☐

Version 9 01/08/2017 p.1 of 4

Current Drug Therapy

7. Is the patient currently on any of the following topical treatments?

Topical pimecrolimus Yes ☐ No ☐ **Topical tacrolimus** Yes ☐ No ☐

8. Please list all the patient's current therapy for any *indication (Please note topical treatments apart from the two listed above are not required)*

DRUG	Date Started (d d m m y y)	DRUG	Date Started (d d m m y y)

Psoriasis Treatment

9. Is the patient currently receiving biologic treatment for their psoriasis? Yes ☐ No ☐

- ☐ **Benepali (etanercept)**
- ☐ **Cimzia (certolizumab pegol)**
- ☐ **Cosentyx (secukinumab)**
- ☐ **Erelzi (etanercept)**
- ☐ **Humira (adalimumab)**
- ☐ **Stelara (ustekinumab)**
- ☐ **Taltz (ixekizumab)**

Commencement date of this episode of biologic therapy: d d m m y y

Is this the patient's first exposure to a biologic agent: Yes ☐ No ☐

Dose:

Frequency:

STELARA ONLY: Provide administration dates

d d m m y y	Batch number

HUMIRA ONLY: Did the patient receive the 80mg loading dose? Yes ☐ No ☐

CIMZIA, COSENTYX, AND TALTZ ONLY: Was the recommended opening schedule followed?

Yes ☐ No ☐

Currently unknown ☐

Cimzia opening schedule: 400 mg at weeks 0, 2 and 4)
Cosentyx opening schedule: 300mg at weeks 0, 1, 2, 3 & 4
Taltz opening schedule: 160mg at week 0, 80mg at weeks 2, 4, 6, 8, 10, and 12)

If 'No', please provide details of deviation from opening schedule:

10. Is the patient currently receiving a small molecule immunomodulator therapy for their psoriasis? Yes ☐ No ☐

DRUG	(Please Tick)	Dose (mg)	Frequency	Date Started (d d m m y y)
Otezla (apremilast)				
Skilarance (dimethyl fumarate)			*Average Daily Dose*	

OTEZLA ONLY: Was the recommended opening schedule followed? Yes ☐ No ☐ Currently unknown ☐

11. Is the patient currently receiving conventional therapy for their psoriasis? Yes ☐ No ☐

DRUG	(Please Tick)	J/cm² or mg	Frequency	Date Started (d d m m y y)	MTX Only: Oral ☐ Sub-Cut ☐
Oral PUVA					
Methotrexate					
Ciclosporin			*Average Daily Dose*		
Acitretin					
Fumaderm			*Average Daily Dose*		
Hydroxycarbamide					

Previous Therapy

12. Please list all previous systemic anti-psoriatic therapy: **If none please tick** ☐

Drug	Start date	Stop date	Stop reason*

***Stop reasons:** Adverse Events, Clinical Trial, Contraindication, Death, Financial Consideration, Inefficacy, Inefficacy and Adverse Events, Other (please provide details), Patient Choice, Patient Non-Compliance, Remission, Titration*

Co-morbidities

13. Has the patient ever had (i.e. required treatment for) any of the following illnesses?

(please tick all that apply) **If none please tick** ☐

Hypertension	Yes	Year of Onset
Hypertension		

Cardiovascular Disease	Yes	Year of Onset
Angina		
Myocardial Infarction		
Stroke / Cerebrovascular Disease		
Peripheral Vascular Disease		
Dyslipidaemia		

Diabetes	Yes	Year of Onset
Type 1		
Type 2		

Autoimmune Disorders	Yes	Year of Onset
Thyroid Disease		
Alopecia Areata		
Vitiligo		
Psoriatic Arthritis		

Thrombosis	Yes	Year of Onset
Deep vein thrombosis		
Pulmonary embolism		
Asthma		
COPD (including chronic bronchitis, emphysema)		

Liver Disease	Yes	Year of Onset
NAFLD (non-alcoholic fatty liver disease, including fatty liver and NASH)		
Alcoholic Liver Disease		
Viral Hepatitis		
Autoimmune Hepatitis		
Inherited Liver Disease (inc. haemochromatosis)		

Kidney Disease	Yes	Year of Onset
Chronic Kidney Disease		
Glomerular Disease		
Renovascular Kidney Disease		
Inherited Renal Disease (polycystic kidney disease)		

Peptic Ulcer	Yes	Year of Onset
Peptic Ulcer		

Demyelination	Yes	Year of Onset
Optic Neuritis		
Multiple Sclerosis		
Transverse Myelitis		
Chronic Inflammatory De-myelinating Polyneuropathy		
Guillain-Barre Syndrome		

Epilepsy	Yes	Year of Onset
Epilepsy		

Peptic Ulcer	Yes	Year of Onset
Peptic Ulcer		

Non-Skin Cancer	Yes	Year of Onset
Please specify type / site:		

Psychiatric	Yes	Year of Onset
Depression		
Anxiety		

Inflammatory Bowel	Yes	Year of Onset
Crohns		
Ulcerative Colitis		

Other (please specify)	Yes	Year of Onset

Skin

Skin Cancer risk factors:

14a) Please indicate Fitzpatrick skin type in box below

Description	Fitzpatrick Skin Type	Please tick
Burns easily, never tans	1	
Burns easily, tans minimally	2	
Burns moderately, tans gradually	3	
Burns minimally, tans well	4	
Rarely burns, tans profusely	5	
Never burns, deeply pigmented	6	

14b) History of prior neoplastic or pre-cancerous lesions? Yes ☐ No ☐

(Please indicate number) and site below)

Type	Site	Number
SCC		
BCC		
Melanoma		
Melanoma in situ		
Actinic keratosis		
Bowen's disease		
Keratoacanthoma		

UV Therapy

15. Has the patient ever had UV therapy? Yes ☐ No ☐ **If YES, please complete the following:**

UV Therapy Details	Yes	No. of Courses	No. of Treatments	Cumulative Dose (J/cm^2)	Data Known to be Accurate?
Broadband UVB					
Narrowband UVB					
TOTAL BODY PUVA					
Oral PUVA					
Topical PUVA					
HAND AND FOOT PUVA					
Oral PUVA					
Topical PUVA					

Lab Values

16. Please complete the following laboratory values (recent i.e. within last 6 months):

LABORATORY VALUES	Result	Date
Haemoglobin count (g/dL)		
White cell count (x10^9/L)		
Platelet count (x10^9/L)		
Creatinine (µmol/L)		
Transaminase ALT (U/L)		
Cholesterol (mmol/L)		
Triglyceride (mmol/L)		
HDL (mmol/L)		

Additional Information

17. What is the patient's current (i.e. at the time that the biologic/systemic agent was started) blood pressure?

Systolic ☐☐☐ mm

Diastolic ☐☐☐ mm

15. What is the patient's current (i.e. at the time that the biologic/systemic agent was started) height, weight and waist circumference?

Height ☐☐☐ cm

Weight ☐☐☐ kg

Waist circumference ☐☐☐ cm

PBQ & QoL Questionnaires

The following patient questionnaires should also be completed:

PBQ ☐

(1)DLQI ☐

EuroQol ☐

CAGE ☐

(2)HAQ ☐

If paediatric patient:

cDLQI ☐

EQ-5D-y ☐

PBQ ☐

(2)cHAQ ☐

(1) It is not essential but a DLQI taken prior to drug commencement is preferred

(2) (Only if patient has a rheumatologist's diagnosis of inflammatory arthritis)

Signature

Please sign and date below:

Name: _____ **Signature:** _____ **Date:** _____

Patient baseline questionnaire

The University of Manchester

BADBIR

PATIENT BASELINE QUESTIONNAIRE

Thank you for your participation in BADBIR. We would be grateful if you could complete the questionnaires below and hand them to your dermatology nurse / doctor

Name: | Date of Birth: | BADBIR ID: *For office use only*

Where were you born? Town: Country:

What is your occupation?

Please tick the one box which best describes you:

☐ Working full-time ☐ Working part-time ☐ Working full-time in the home ☐ Student

☐ Unemployed but seeking work ☐ Not working due to ill health/disability ☐ Retired

Which of these ethnic groups do you belong to?

☐ White ☐ Indian ☐ Pakistani ☐ Bangladeshi ☐ Chinese

☐ Black-African ☐ Black-Caribbean ☐ Black-British ☐ Black-other

☐ Other Please specify

Do you have an occupation or hobby which is mainly outdoors? ☐ Yes ☐ No

Have you ever lived in a tropical/subtropical (hot/sunny climate) country? ☐ Yes ☐ No

Have you EVER smoked more than one cigarette a day? ☐ Yes ☐ No

If you have ever smoked, what was the average number of cigarettes /day? ☐ Cigarettes per day

Age started smoking ☐ years **Age stopped smoking** ☐ years

Do you CURRENTLY smoke more than one cigarette a day? ☐ Yes ☐ No

If YES, how many cigarettes do you smoke each day? ☐ Cigarettes per day

Do you drink alcohol? ☐ Yes ☐ No

If yes, how many units do you drink in an average week?
For guidance please refer to the table below ☐

Alcoholic Drink	No. of units
A pint of ordinary beer/lager (4%)	2.3
A pint of strong lager	3
A standard (175ml) glass of wine	2
A large (250ml) glass of wine	3
A small (25ml) glass of spirits	1
A 275ml bottled alcopop	1.5

Version 5 (*abridged*) 30/11/2007 **Signature:** _____ **Date:** ____/____/____

Dermatology life quality index questionnaire

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date: Score: ☐

Name: Diagnosis:

Address:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

CAGE questionnaire (cut down, annoyed, guilty, early morning)

Patient Name	Date Completed

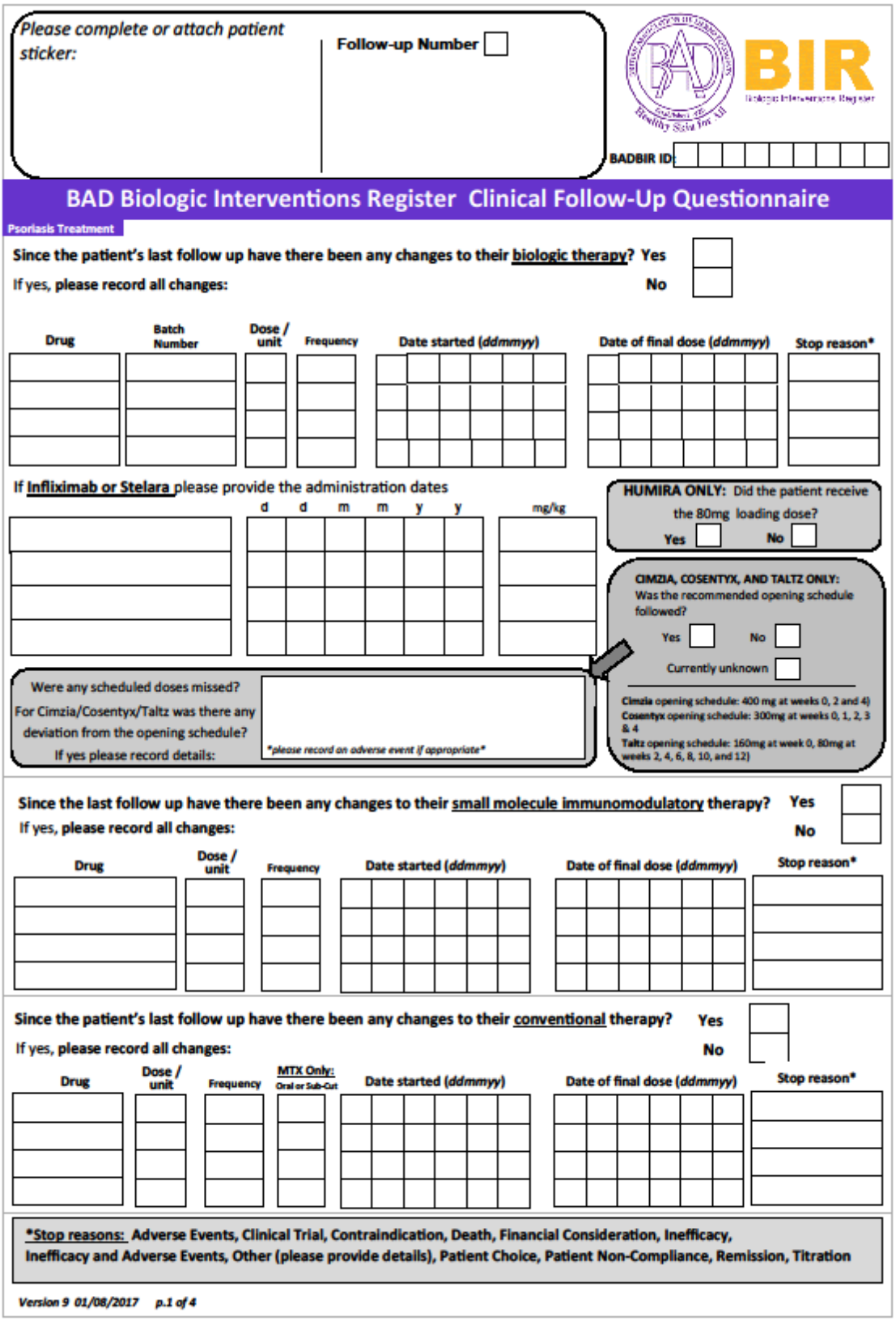
CAGE Questionnaire (Cut down, Annoyed, Guilty, Early morning)

Alcohol Intake:

1. Have you ever felt you should cut down on your drinking?	Yes	☐	1
	No	☐	0
2. Have people annoyed you by criticising your drinking?	Yes	☐	1
	No	☐	0
3. Have you ever felt bad or guilty about your drinking?	Yes	☐	1
	No	☐	0
4. Have you ever had a drink first thing in the morning (as an "eye opener") to steady your nerves or to get rid of a hangover?	Yes	☐	1
	No	☐	0

Appendix 11: Follow-up questionnaires

Clinical follow-up questionnaire



Please complete or attach patient sticker:

Follow-up Number ☐

BADBIR ID:

BAD Biologic Interventions Register Clinical Follow-Up Questionnaire

Psoriasis Treatment

Since the patient's last follow up have there been any changes to their biologic therapy? Yes ☐ No ☐

If yes, **please record all changes:**

Drug	Batch Number	Dose / unit	Frequency	Date started (*ddmmyy*)	Date of final dose (*ddmmyy*)	Stop reason*

If **Infliximab or Stelara** please provide the administration dates

	d d m m y y	mg/kg

HUMIRA ONLY: Did the patient receive the 80mg loading dose? Yes ☐ No ☐

CIMZIA, COSENTYX, AND TALTZ ONLY: Was the recommended opening schedule followed? Yes ☐ No ☐ Currently unknown ☐

Cimzia opening schedule: 400 mg at weeks 0, 2 and 4)
Cosentyx opening schedule: 300mg at weeks 0, 1, 2, 3 & 4
Taltz opening schedule: 160mg at week 0, 80mg at weeks 2, 4, 6, 8, 10, and 12)

Were any scheduled doses missed? For Cimzia/Cosentyx/Taltz was there any deviation from the opening schedule? If yes please record details:

please record on adverse event if appropriate

Since the last follow up have there been any changes to their small molecule immunomodulatory therapy? Yes ☐ No ☐

If yes, **please record all changes:**

Drug	Dose / unit	Frequency	Date started (*ddmmyy*)	Date of final dose (*ddmmyy*)	Stop reason*

Since the patient's last follow up have there been any changes to their conventional therapy? Yes ☐ No ☐

If yes, **please record all changes:**

Drug	Dose / unit	Frequency	MTX Only: Oral or Sub-Cut	Date started (*ddmmyy*)	Date of final dose (*ddmmyy*)	Stop reason*

***Stop reasons:** Adverse Events, Clinical Trial, Contraindication, Death, Financial Consideration, Inefficacy, Inefficacy and Adverse Events, Other (please provide details), Patient Choice, Patient Non-Compliance, Remission, Titration

Version 9 01/08/2017 p.1 of 4

UV Therapy

Since the patients last follow-up have they had any UV therapy? Yes ☐
If yes, please complete the following: No ☐

UV Therapy Details	Yes	No. of Courses	No. of Treatments	Cumulative Dose (J/cm^2)	Data Known to be Accurate?
Broadband UVB					
Narrowband UVB					
TOTAL BODY PUVA					
Oral PUVA					
Topical PUVA					
HAND AND FOOT PUVA					
Oral PUVA					
Topical PUVA					

Concomitant Therapy

Since the patient's last follow up have they had any changes to their concomitant therapy? Yes ☐
If yes, please complete the following: *(please note we do not need details of topical therapy for psoriasis except for tacrolimus and pimecrolimus)* No ☐

Drug	Start date	Stop date	Are these dates estimated?

Lab Values

Please complete the following laboratory values (recent i.e. within last 6 months):

LABORATORY VALUES	Result	Date
Haemoglobin count (g/dL)		
White cell count (x10^9/L)		
Platelet count (x10^9/L)		
Creatinine (µmol/L)		
Transaminase ALT (U/L)		
Cholesterol (mmol/L)		
Triglyceride (mmol/L)		
HDL (mmol/L)		

FUP7 + : Lab Values not required

Adverse Events

Since date of last data entry has your patient experienced any adverse events)? Yes ☐ No ☐

An adverse event (AE) is defined as any medically untoward event occurring in a patient whether or not related to any treatment or medication

A serious adverse event (SAE) is defined by the classifications in the box below

Please enter details of ALL adverse events (both serious and non-serious) from this follow-up period

Event No.	Short description of event (please record diagnosis if available)	Description of event	Start date	Start Date Estimated?	Stop date	Stop Date Estimated?	Is the event ongoing?	Is the event related to biologic therapy? *Yes, No or Possibly* *Not required for conventional cohort patients*	Yellow Card Sent?	Is the event a SAE ? If yes please select code (see below)	Is the event an ESI? If yes please select from list (see below)	Outcome of the event?
								If 'Yes' Name of Biologic:______		If 'Hospitalisation' Admission Date:______ Discharge Date:______		Resolved ☐ Resolved w/Sequelae ☐ Not Resolved ☐ Unknown ☐ Death ☐
								If 'Yes' Name of Biologic:______		If 'Hospitalisation' Admission Date:______ Discharge Date:______		Resolved ☐ Resolved w/Sequelae ☐ Not Resolved ☐ Unknown ☐ Death ☐
								If 'Yes' Name of Biologic:______		If 'Hospitalisation' Admission Date:______ Discharge Date:______		Resolved ☐ Resolved w/Sequelae ☐ Not Resolved ☐ Unknown ☐ Death ☐
								If 'Yes' Name of Biologic:______		If 'Hospitalisation' Admission Date:______ Discharge Date:______		Resolved ☐ Resolved w/Sequelae ☐ Not Resolved ☐ Unknown ☐ Death ☐
								If 'Yes' Name of Biologic:______		If 'Hospitalisation' Admission Date:______ Discharge Date:______		Resolved ☐ Resolved w/Sequelae ☐ Not Resolved ☐ Unknown ☐ Death ☐

Code	SAE Classification
1	Death
2	Hospitalisation
3	IV Anti-biotics/virals/fungals
4	Significant loss of function or disability
5	Congenital malformation
6	Was in any way life threatening
7	Medically Important Event

If any of the events you have listed include any of the following, an Event of Special Interest (ESI) form needs to be completed:

- *Aplastic anaemia, pancytopaenia or serious neutropenia*
- *Cerebrovascular Accident (CVA)*
- *Hepatitis B Reactivation*
- *Lymphoproliferative Disease*
- *Malignancy (not inc. skin)*
- *Melanoma / Skin Cancer (inc. Bowens Disease)*
- *Drug misuse, abuse, overdose and medication*
- *Myocardial Infarction/Acute Coronary Disease*
- *Pregnancy*
- *Progressive Multifocal Leukoencephalopathy*
- *Pulmonary Embolism*
- *Serious Congestive Heart Failure*
- *Serious Hepatic Dysfunction/Failure*
- Serious Hypersensitivity Reaction
- Serious Infection (excl. TB)
- Serious Lupus/Lupus like illness
- Serious Psoriasis Flare *(Overnight Hospitalisation Only)*
- Serious Skin Reaction
- Surgery *(Overnight Hospitalisation Only)*
- Tuberculosis (Not Latent)

Version 9 01/08/2017 p.3 of 4

Current Disease Severity

Please indicate the current disease severity (i.e. at the time the patient started the new drug)

BSA ☐☐ ***Only if the patient has pustular psoriasis***

Date of BSA ...../...../.....

Please details of all PASI's that have been completed since the patients last follow-up.

PASI	Date of PASI	Psoriasis Global Assessment

Psoriasis Global Assessment score:

- Severe
- Moderate to severe
- Moderate
- Mild
- Almost clear
- Clear

Has the patient been diagnosed with psoriatic arthritis by a rheumatologist? **Yes** ☐ **No** ☐

if this is a new diagnosis please remember to add this as an adverse event

Additional Information

What is the patient's current weight and waist circumference?

Weight ☐☐☐ kg

Waist circumference ☐☐☐ cm

FUP9 + : Weight / Waist not required

If the patient is under 16 year of age on the date of this follow-up, please provide a height measurement: ☐☐☐ cm

Patient Follow-up Questionnaire

The patient questionnaire should also be completed containing:

Occupation Qus ☐
DLQI ☐
EuroQol ☐

Lifestyle Qus ☐
CAGE ☐
***HAQ** ☐

If paediatric patient:

cDLQ ☐
EQ-5D-y ☐

***cHAQ** ☐

FUP 7+ : Patient Questionnaire is not required

(*Only if patient has a rheumatologist's diagnosis of inflammatory arthritis)

Signature

Please sign and date below:

Clinician's signature:_____ **Date:**_____

Event of special interest: Cerebrovascular accident (CVA) form

PATIENT:	BADBIR ID:	
HRN:	DOB:	
BIOLOGIC / CONVENTIONAL TREATMENT:		

Event of Special Interest: Cerebrovascular Accident (CVA)

Any Further Event Details

Was the stroke haemorrhagic ☐ YES ☐ NO ☐ DON'T KNOW

Or ischaemic ☐ YES ☐ NO ☐ DON'T KNOW

Was the patient thrombolysed? ☐ YES ☐ NO ☐ DON'T KNOW

Does the patient have atrial fibrillation? ☐ YES ☐ NO ☐ DON'T KNOW

Or paroxysmal atrial fibrillation? ☐ YES ☐ NO ☐ DON'T KNOW

Was a CT/MRI done?
(If yes, please attach report) ☐ YES ☐ NO ☐ DON'T KNOW

Did signs/symptoms fully resolve? YES ☐ NO ☐ DON'T ☐ KNOW

If so, did they resolve within: 24 ☐ hours ☐ 1 week ☐ More than one week

If you have any questions please call the Register office on: 0161 306 1911

Form completed By: _____

On: ____/____/____

Please note this ESI form needs to be entered directly onto the BADBIR database in the adverse section

Event of special interest: Myocardial infarction/acute coronary disease form

PATIENT: **BADBIR ID:**

HRN: **DOB:**

BIOLOGIC / CONVENTIONAL TREATMENT:

Event of Special Interest: Myocardial Infarction / Acute Coronary Disease

Rise in cardiac markers eg. troponins? YES ☐ NO ☐ ☐ DON'T KNOW

Trop T/ Trop I Level: _____

Did the patient have ischemic symptoms? ☐ YES ☐ NO ☐ DON'T KNOW

ECG findings:

Were there any ischemic changes YES ☐ NO ☐ DON'T KNOW ☐

Were there any new Q waves YES ☐ NO ☐ DON'T KNOW ☐

Was the patient thrombolysed? YES ☐ NO ☐ ☐ DON'T KNOW

Did they receive angioplasty?

YES (date __/___/_____) ☐ NO ☐ DON'T KNOW ☐

Did have any other cardiac intervention?

YES ☐ NO ☐ DON'T KNOW ☐

If Yes Please Specify Details:

If you have any questions please call the Register office on: 0161 306 1911

Form completed By: _____

On: ____/____/____

Please note this ESI form needs to be entered directly onto the BADBIR database in the adverse section