Skin Disease and Vitamin D

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Abstract

Background

There is a growing interest in the role of vitamin D beyond its effect on bone health. The vitamin D receptor is widely expressed in many different tissues, including the skin.

Aim

The aim was to investigate the association between 25-hydroxyvitamin D and cutaneous lupus erythematosus, and the effect of vitamin D on psoriasis. Two additional studies about the population prevalence of cutaneous lupus and the cardiovascular risk of psoriasis were undertaken.

Methods

Patients with cutaneous lupus were identified from multiple sources from both the hospital and the community. The database compiled was then used to clinically assess both the scarring and the activity of cutaneous lupus in association with 25-hydroxyvitamin D status.

A randomised, placebo-controlled study of the effect of oral 100,000 IU monthly Vitamin D_3 (cholecalciferol) was undertaken with participants who had psoriasis and had been recruited to a larger study called the Vitamin D assessment study.

Results

One hundred and forty-five patients with cutaneous lupus were identified. Māori and Pacific people were found to have a higher prevalence of all types of cutaneous lupus compared with the European population [relative risk 2.47 (95% CI: 1.67–3.67)] and especially discoid lupus [relative risk 5.96 (95% CI: 3.06–11.6)]. No relationship was found between cutaneous lupus (either active disease or scarring) and 25-hydroxyvitamin D levels.

Sixty-five patients with mild psoriasis were recruited. The mean Psoriasis Area Severity Index was 3.0 and 3.3 in the placebo and active group respectively. No improvement in psoriasis was recorded by the addition of vitamin D_3 when assessed by the Psoriasis Area Severity Index, Global Physician's Assessment, Dermatology Life Quality Index or the Psoriasis Disability Index ($p > 0.05$).

There was no increase in cardiovascular risk in the psoriasis participants ($p > 0.05$).

Conclusions

25-hydroxyvitamin D status is not a significant factor for cutaneous lupus. Further research is needed to examine why Māori and Pacific peoples have high rates of cutaneous lupus.

Oral vitamin D_3 is not a therapeutic option for patients with mild psoriasis, and the low cardiovascular risk of a New Zealand patient cohort with mild psoriasis is confirmed.

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Contribution of Study Investigators

Professor Robert Scragg, Department of Epidemiology and Biostatistics, The University of Auckland, was the primary supervisor of this thesis and Honorary Associate Professor Marius Rademaker, Dermatologist, Waikato Hospital, was the secondary supervisor.

The candidate was principally responsible for the ethics approval, design, data extraction, recruitment, participant assessment and analysis of the cutaneous lupus prevalence study and the study of the association of 25-hydroxyvitamin D with cutaneous lupus. Professor Carlos Camargo, Harvard Medical School, Boston, USA, gave advice about questionnaire design for the psoriasis substudy. The candidate was responsible for the protocol, the questionnaire design, the choice of assessment methodology, all clinical assessments of the participants and the analysis of the ViDA psoriasis study. Professor Andrew Finlay, Cardiff University, UK, gave permission for use of the Dermatology Quality of Life questionnaire and the Psoriasis Disability Index. Dr John Sluyter, Postdoctoral Research Fellow Department of Epidemiology and Biostatistics, The University of Auckland, provided the arterial waveform data and the candidate undertook the analysis.

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Abbreviations

A glossary of commonly used abbreviations in this thesis is below.

ACLE	Acute Cutaneous Lupus Erythematosus
AIx	Augmentation Index
ANA	Antinuclear Antibody
BMI	Body Mass Index
CI	Confidence Interval
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CMDHB	Counties Manukau District Health Board
DLE	Discoid Lupus Erythematosus
DLQI	Dermatology Life Quality Index
ENA	Extractable Nuclear Antibody
EPI	Excess Pressure Integral
IL-17	Interleukin-17
PASI	Psoriasis Area and Severity Index
PDI	Psoriasis Disability Index
PGA	Physician's Global Assessment
SCLE	Subacute Cutaneous Lupus Erythematosus
SD	Standard Deviation
SLE	Systemic Lupus Erythematosus
VDBP	Vitamin D Binding Protein
VDR	Vitamin D Receptor
ViDA	Vitamin D Assessment Study
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B

25-Hydroxyvitamin D use is directly transcribed from referenced papers and implies 25-Hydroxyvitamin D_3 and 25-Hydroxyvitamin D_2. 25-Hydroxyvitamin D_3 is used when it is specifically needed or directly referenced from papers.

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Chapter 1 Thesis Introduction

The role of vitamin D is currently the subject of intense interest in a large variety of diseases and the primary source is through sun exposure of the skin. Vitamin D has been recognised as having a role beyond bone and calcium metabolism (see Chapter 3, Section 3.1.2). This thesis primarily examines the role of vitamin D in two dermatological conditions. These are cutaneous lupus and psoriasis. Psoriasis is a common inflammatory skin disease that has a population prevalence of 1–2% and is improved by sunlight, whereas cutaneous lupus is a less common skin disease that is exacerbated by sun exposure (1).

The framework of this thesis is a six-year period from 2009 to 2015 encompassing four studies. The first two studies are about cutaneous lupus. Patients with cutaneous lupus needed to be identified in order to undertake a study of any possible association with vitamin D. The community chosen was South Auckland, New Zealand, as this was the author's place of work (Counties Manukau District Health Board [CMDHB]) and the population community is ethnically diverse, allowing a prevalence analysis by ethnicity. The patients with cutaneous lupus were identified within the district health board boundary. The population demographics of the district health board are well characterised, which facilitated the prevalence study of cutaneous lupus. Having identified the patient population, the second study explored cutaneous lupus and its association with vitamin D status.

The second two studies on psoriasis derive from a large, Auckland-wide, community-based, blinded, placebo-controlled study called the Vitamin D Assessment study shortened to the acronym ViDA. This study enrolled 5,110 participants from Auckland, to assess the potential health benefits of vitamin D_3 supplementation on cardiovascular, respiratory and bone health. The ViDA study was funded by the New Zealand Health Research Council and the Accident Compensation Corporation. Participants from this study, who had psoriasis, were invited to enrol in a substudy to observe the effect of supplementation on their skin disease. The participants were observed at regular intervals for 12 months and data collection took approximately 18 months.

Therefore, the overall objectives of this thesis were:

1. To perform a comprehensive literature review placing skin, vitamin D, light, heliotherapy, phototherapy, cutaneous lupus and psoriasis in their historic and modern context, both internationally and in New Zealand
2. To undertake a prevalence survey of cutaneous lupus in the CMDHB, South Auckland, New Zealand
3. To examine whether vitamin D status was related to the presence, activity or scarring of cutaneous lupus in South Auckland, New Zealand
4. To determine whether vitamin D supplementation is an effective treatment for participants of the ViDA study who had psoriasis
5. To examine the cardiovascular risk of participants of the ViDA study who had psoriasis.

The thesis is structured as nine chapters and this is Chapter 1. Chapter 2 is a historical review of the literature discussing evolutionary biology and its relevance to the skin and vitamin D (Objective 1). Vitamin D, psoriasis and cutaneous lupus are complex issues. The historic review, therefore, starts in prehistory as this is relevant to the skin and moves through the ages concluding in the last century. It is important to understand evolutionary biology and human migration out of Africa, as this is directly relevant to vitamin D in the modern New Zealand population. Chapter 3 describes vitamin D physiology, the controversial subject of “normal” levels of vitamin D and the literature describing levels in New Zealand (Objective 1). Chapter 4 is the literature review, mainly focusing on cutaneous lupus and psoriasis, particularly within the areas of study of this thesis (Objective 1). A section is included on other skin diseases and vitamin D, as skin is central to vitamin D. The thesis would not be comprehensive without a brief mention of the other skin diseases discussed in the dermatological literature in relation to vitamin D (Objective 1). Chapter 5 is split into two sections (Objectives 2 and 3). The first describes the prevalence study and the second describes the study examining vitamin D levels and cutaneous lupus. Chapter 6 describes the double-blind, placebo-controlled study on the effect of vitamin D supplementation on psoriasis (Objective 4). Severe psoriasis has become recognised as an independent risk factor for cardiovascular disease (2) so it was possible to examine this risk in the ViDA psoriatic participants. All ViDA participants had a number of cardiovascular variables recorded, including arterial waveforms. Chapter 7 (Objective 5) describes the study of psoriasis and cardiovascular risk. Chapter 8 is the thesis discussion putting the new findings in context with other relevant research. Finally, Chapter 9 is a summary of the conclusions.

Chapter 2 Historic Review

2.1 Introduction

Vitamin D, sunlight and human behaviour are inextricably intertwined subjects. The major source of vitamin D is through the interaction of sunlight, especially the wavelength ultraviolet B (UVB), on the skin. Vitamin D has been a driver of the evolutionary biology of human skin, arising from the migration of humans out of Africa. The early Polynesians, through their mastering of sea travel, outstripped the ability of evolution to adapt skin colour to the environment, with potential implications for vitamin D synthesis that have direct relevance to vitamin D levels in the mixed ethnicity of contemporary New Zealand society. Chapter 2 contains an historical review examining the medical use of light in earliest recorded human history and then moves forward to the 20th century to chronicle the use of light with the introduction of vitamin D therapy. A subsection is specifically dedicated to Niels Finsen, who was the founder of light therapy for cutaneous tuberculosis (lupus vulgaris), for which he was awarded a Nobel Prize in 1903.

2.1.1 Evolution, Skin Colour and the Migration of Early Humans

It is generally accepted that modern humans (*Homo sapiens*) originated from central Africa (3). Three million years ago protohumans, such as *Australopithecus afarensis*, led a sedentary life in a wooded environment. Food such as fruit, leaves, seeds and water was in abundance, so significant or prolonged physical exertion was not needed to obtain sufficient nutrition. Using data from fossil records to study climate change, it has been recognised that approximately 3 million years ago the habitat of protohumans changed as the earth became cooler and drier. In response to diminishing food supplies, protohumans needed to adapt to survive, by leading a less sedentary life in search of adequate nutrition. Approximately 2.6 million years ago the archaeological evidence records the use of stone tools and butchered animal bones. Meat is a richer source of nutrient than vegetable matter, but is scarce and mobile; therefore, more energy expenditure is required to obtain this nutrition. With greater energy expenditure came the need for greater thermal regulation, particularly cooling, as the brain is especially temperature sensitive. Therefore, the need to maintain temperature regulation was a strong evolutionary drive, and effective temperature regulation also permitted an increase in brain size. Hand in hand with temperature regulation came bipedalism, which was the switch from a four-legged to a two-legged existence. Bipedalism carries significant competitive advantages of speed, height and the use of tools. *Homo ergaster*, 1.6 million years ago, was the first hominid to have elongated limbs capable of sustained walking and running (4).

There is an evolutionary advantage to hairlessness. The modern-day chimpanzee is our closest living relative. Chimpanzees have pink skin covered with black fur. The hominids are believed to have shared this phenotype. Hair provides effective sun protection and thermoregulation for a sedentary lifestyle. The most efficient evaporative cooling of sweat occurs at the skin surface and then water vapour is transferred through the fur. Dry fur also protects the body from external environmental heat gain. If fur becomes wet, evaporation occurs at the surface of the fur and not at the skin, and therefore heat from the cutaneous vessels has a barrier to its site of loss. Consequently, there is an advantage to hairlessness when there is a need for significant heat loss, which will occur with exercise (5).

In modern humans there are three types of sweat glands: eccrine, apocrine and apoeccrine. They secrete fluid directly into the duct. These glands vary in type, density and anatomical location. The eccrine glands are the most important for temperature control. Approximately 1.6 to 4 million are distributed over most of the body surface. Eccrine sweat is a sterile dilute electrolyte solution. Apocrine glands are limited in their distribution to axillae, anogential and periumbilical skin, nipples and vermillion border, and they connect by a stretched duct into the follicular canal. Apocrine sweat is a sterile viscous oily fluid. Apoeccrine glands are confined to the adult axilla. Sebaceous glands are associated with hair follicles and produce sebum, a yellow viscous fluid, by holocrine secretion. This is cellular disintegration with release of sebum into the duct, through a different mechanism from that of the sweat glands. The chimpanzee, gorilla and baboon have heavy fur coats. These animals have thermal apocrine glands and eccrine glands. Therefore, it is inferred that the ancestral great apes were able to “supply” eccrine glands to the protohumans. These coats provide physical protection and are efficient cooling systems using apocrine sweat when dry but are not effective cooling systems when wet from sweat production. Hair is disadvantageous for prolonged physical exercise. There are no thermal apocrine glands that are not associated with hair follicles. Natural selection, therefore, drove the loss of hair and apocrine glands to favour the development of an eccrine sweating for effective temperature control in concert with bipedalism (5).

The central equatorial African savannah is a high ultraviolet (UV) environment and a lack of hair results in UV-induced damage through lack of sun protection. Therefore, evolutionary pressures worked to provide the needed protection and this may have been driven by the requirement for folic acid protection. Folic acid is an essential vitamin needed for numerous biological functions, including DNA synthesis and repair, red blood cell production and spermatogenesis. In humans, disorders associated with lack of folic acid include megaloblastic anaemia, peripheral neuropathy and, in pregnancy, foetal neural tube defects. Folic acid deficiency is also associated with multiple defects in non-human mammals. In the human body, folate (the naturally occurring form) is sensitive to UV-induced degradation in the skin. UV-induced folate degradation has been demonstrated in light-skinned patients exposed to natural sunlight. Therefore, there was a strong evolutionary pressure to protect the skin and this was achieved by the production of melanin (6). An alternative and perhaps complementary theory was that darker skin also evolved as hominids realised that significant quantities of food could be found along waterways and especially the littoral zones. Hominids, who like other animals usually had no need to venture out at midday, would be forced by the tide cycle to forage when the tide allowed and therefore darker skin provided more protection (7).

Melanin is produced in the melanocyte. The melanocyte is a cell derived from the neural crest that, in the skin, resides in the basal layer of the epidermis. The production of melanin is complex and occurs in the intracytoplasmic organelle called the melanosome. This moves along the dendritic process of the melanocyte and is then transferred to the keratinocyte. It is the activity, and not the number, of melanocytes that determines skin colour: darkly pigmented skin has melanosomes with a heavy deposition of melanin compared with fair skin, which has minimal melanin deposition. There are two major forms of melanin produced by melanocytes: brown-black eumelanin and yellow-red phaeomelanin. Melanin attenuates UV radiation by absorption, dissipating it as heat. Melanocortin 1 receptor (MC1R) is a membrane-bound receptor on melanocytes and is one of the most important regulators of melanin production (1).

The MC1R gene is mapped to chromosome 16q24. There is almost no variation in this coding region in African populations, supporting the view of strong selective pressure to maintain dark skin colour in the African environment (8, 9). Therefore, at some point in the transition from the hairy to the hairless state, evolutionary pressure would have acted to support the selection of the MC1R alleles producing skin pigmentation. Genetic modelling suggests that this gene variant found in Africans may have emerged 1.2 million years ago, which is in keeping with the archaeological record of the switch to bipedalism (10).

The vitamin D binding protein (VDBP) has also been subject to evolutionary pressure that can be considered a continuous process of structural modification from primates (11). The gene was the target of locally exerted selective pressure driving different haplotypes in distinct human populations (12). A study relevant to evolution was published by Powe et al (13) examining the ethnic differences between the VDBP of black and white Americans. There are lower levels of 25-hydroxyvitamin D in the African-American population but higher bone density compared with that of the white population. However, there are lower levels of VDBP in African-Americans, which result in bioavailable levels of 25-hydroxyvitamin D equivalent to whites. There are different polymorphisms of the VDBP, with GC1F most abundant in persons of African ancestry and GC1S most abundant in European populations. The affinity of the two VDBPs is different for vitamin D, with GC1F being greater than GC1S, and it is possible that during evolution the most abundant form of the VDBP in dark skin was able to transport vitamin D_3 more efficiently from the skin to the liver for its metabolism to 25-hydroxyvitamin D_3. However, the methodology and therefore the conclusions of the Powe study have been challenged in a series of letters to the editor. The criticisms include not considering the role of the renal proximal tubule, the methodology of calculating the bioavailable 25-hydroxyvitamin D and the monoclonal antibodies used (14, 15).

2.1.2 Colonisation of the Pacific, Ultraviolet Light Exposure and Vitamin D

The exact method, mode and timing of human dispersion out of central Africa are uncertain. These uncertainties aside, humans migrated north probably through modern-day Egypt and the eastern Mediterranean into Europe and east into Asia, perhaps following the coastline. The ancient coastline was different from what it is today, as sea levels were lower because of large quantities of water locked in polar ice caps. Migration of hominids in eastern Asia was occurring during the Pleistocene era (2.6 million to 11,700 years ago) (3). Movement further east into the Pacific may have occurred from Taiwan (the “out of Taiwan model”) or possibly from Wallacea, which is a geographical group of islands between the Asian and Australian continental shelves. The last major migration of humans was into the remote eastern Pacific during the Holocene era (10,000 years ago to current) (16). The Pacific rat (*Rattus exulans*) travelled with ancient humans and can be used as a proxy to estimate the time of arrival at a given location. Radiocarbon dating of distinctive rat-gnawed seeds and rat bones from different locations around New Zealand show that the rat was established in New Zealand by approximately 1280 AD and there is no evidence to suggest the presence of rats during the preceding millennium (17). This time frame is supported by mitochondrial DNA studies of Māori, whose founder population of women arrived in the waka (canoes) numbering 170–230 (18).

As humans migrated away from the central equatorial African climate to different latitudes, exposure to UVB diminished and therefore the ability to produce sufficient vitamin D. Highly melanised skin requires

longer exposure to UVB when the intensity is reduced, in order to produce sufficient vitamin D, and therefore evolutionary selective pressure favoured the loss of melanin. Depigmentation was evolved through different mechanisms in northern Europeans, modern East Asians and Neanderthal humans (19-22). There are many examples of parallel and convergent evolution in nature, including depigmentation in the evolution of human skin.

There is a strong correlation of skin reflectance with latitude and UV radiation. Interestingly, in all populations studied, females are found to have lighter skin than males. The lighter skin of females may be due to the evolutionary pressure to produce greater quantities of vitamin D during pregnancy and lactation (6). New Zealand lies approximately between latitude 35° and 46° south. Wellington sits at 41°19' south. The potential for the synthesis of previtamin D_3 (see Chapter 3, Section 3.1.1) in the skin has been estimated from average annual UV minimal erythemal doses. The minimal erythemal dose is the quantity of UV radiation required to produce a barely perceptible reddening of the skin. New Zealand and Southern Australia, including Tasmania, fall into a zone where there is insufficient UV radiation to catalyse the formation of previtamin D_3 in moderately and highly melanised (Fitzpatrick type 5 and 6) skin. In lightly pigmented (Fitzpatrick type 3) skin, these areas fall into the category for which there is insufficient UV radiation during at least one month of the year to produce vitamin D_3 (6). Therefore, approximately 700 years ago the earliest Polynesian colonisers of New Zealand entered a UV environment setting the stage for relative vitamin D deficiency (see Chapter 3, Section 3.1.3.1).

2.2 Historic Review of Light, Vitamin D and the Skin

This section of Chapter 2 reviews the history of light treatment and vitamin D as it relates to the skin from the earliest recorded history up to the 20th century. The use of natural sunlight, and then the development of medical phototherapy, has a long history. The earliest records are from the Egyptian papyri, and light in its modern form is utilised in phototherapy cabinets, predominately using specialised bulbs that emit a narrowband of UVB at 311 nm.

The use of oral vitamin D for skin disease became popular at the beginning of the 20th century, but its use declined with the advent of topical vitamin D analogues. In the 21st century there has been a resurgence of interest in vitamin D as evidence has accumulated that it may have a far greater role than expected in human physiology and disease.

2.2.1 Ancient History

The association between sun exposure and skin disease extends back to prehistory. One of the earliest medical records comes from the Papyrus Ebers, written in approximately 1500 BC but containing medical texts copied from as early as 3400 BC. The papyrus was said to have been found between the legs of a mummy and it is considered one of the most important medical papyri of ancient Egypt. The use of sunlight to "charm away alopecia" is recorded in Cyril P Bryan's 1930 translation from German of the Papyrus Ebers. The charm reads, "O Shining One, Thou who hoverest above! O Xare! O Disc of the Sun! O Protector of the Divine Neb-apt!" The charm was to be spoken over iron, red-lead, onions, alabaster and honey (23). Heliopolis was the centre of sun worship in ancient Egypt of the sun god Ra (Re). This ancient city has been buried under north-east modern-day Cairo.

Moving forward to the Greek era, Hippocrates wrote *On Airs, Waters and Places* in 400 BC. It is a document that describes the effects of the physical environment, including "the winds, the hot and the cold" and "the qualities of the waters" on human health and disease. He describes the Scythian race as "tawny from the cold, and not the intense heat of the sun, for the whiteness of the skin is parched by the cold, and becomes tawny" (24). The Scythians were equestrian tribes inhabiting the central Eurasian steppes. In early Arabic literature, in approximately 1100 AD, an Arabic physician called Dr Ibn al-Bitar wrote a book entitled *Kitab al-Jimi' li-mufradat al-adwija wa-l-agiya* (The Comprehensive Book on Materia Medica and Foodstuffs), which discusses a treatment for vitiligo with oral extracts of a weed that grows on the Nile Delta called *Ammi majus* and sunlight (25).

The use of light and skin disease also extends to early Indian medical texts, including hymn 23 of the ancient Vedic text of Atharva Veda, "A Charm against Leprosy", which reads, "O plant, thou sprangest up at night, dusky, dark coloured, black in hue! So, Rajani, re-colour thou these ashy spots, this leprosy". The plant is believed to have been *Psoralea corylifolia* and ingestion of its seeds in combination with sunlight was believed to be a treatment for this leucoderma. There is debate as to whether this refers to leprosy or vitiligo (25, 26).

2.2.2 Modern History

In 1877 Dr Arthur Downes and Mr Theo Blunt published their paper called “Researches on the Effect of Light upon *Bacteria* and other Organisms” in the journal *Proceedings of the Royal Society of London*. In this pivotal paper, the authors set out to ascertain whether “light could be shown to exert any appreciable influence, favourable or the reverse, upon the development of Bacteria and other organisms”. They showed that light exposure inhibited bacterial and fungal growth. They described a series of observations using test tubes containing “Pasteur’s solution” and measured the quantity of bacteria by the turbidity of the solution. The first observation was of eight test tubes placed outside a window facing south-east about 30 feet above the ground. Four of the tubes were protected from sunlight with a thin lead sheet and four were exposed. The bare tubes remained “quite clear”. In further experiments they also demonstrated that light may “retard or altogether prevent the appearance of mycelial fungi” (27).

The dawn of modern phototherapy had commenced. In a review of phototherapy published in 1901 in *Scientific American*, the question was asked “whether it would not be possible to treat and cure certain skin diseases considered as parasitic, and microbian, by the exclusive use, on the contrary, of the chemical violet radiations, which are so active in the destruction of microbes” (28).

2.2.2.1 Niels Ryberg Finsen

In 1903 Niels Finsen was awarded the Nobel Prize in Medicine. His citation reads, “in recognition of his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light radiation, whereby he has opened a new avenue for medical science” (29).

Lupus vulgaris is a cutaneous infection of the skin by *Mycobacterium tuberculosis*. It can be a primary infection of the skin or occur as a secondary infection from haematogenous or lymphatic spread from a tuberculous focus. As the infection spreads through the skin, substantial tissue destruction occurs over a number of years, leading to disfigurement. The head and neck are the most commonly affected sites. There are a number of clinical presentations, including plaque or planar, ulcerative or mutilating, vegetating, tumour like and papulonodular (1). In the time of Niels Finsen, lupus vulgaris was a common disorder with a prevalence of approximately 1–2% of the population (30).

Niels Finsen was born on the Faroe Islands on 15 December 1860 and he studied medicine in Copenhagen, graduating in 1890. Finsen observed that smallpox lesions of the face and hands that were exposed to sunlight became pitted, whereas the covered areas did not scar. Therefore, Finsen advised excluding the sun’s blistering chemical rays with heavy red curtains that permitted only warming, non-blistering red rays to enter, which subsequently reduced scarring (31).

In 1896 Finsen founded the Lysinstitut, which was later named the Finsen Institute. In that year he treated a friend, Niels Mogensen, who had lupus vulgaris, with a “chemical rays” lamp, and within a few months the lesions had completely resolved. He then developed a focusable carbon arc lamp with quartz filters and went on to treat over 800 patients with lupus vulgaris, and 80% were cured. This was a major breakthrough at a time prior to antibiotic therapy and led to his Nobel Prize. Finsen was too unwell to attend the prize ceremony, as he had Niemann-Pick disease and was confined to a wheelchair. He died a year after receiving his prize at the age of 44 years (30-32).

Finsen believed that the short wave UV light (UVB) was the most efficient in treating lupus vulgaris. However, an examination of his equipment a century later suggested there was a relative lack of UVB output and that ultraviolet A (UVA) may have been more significant (30). A modern scientific validation of Finsen's work is discussed in Chapter 4, Section 4.4.

2.2.3 Heliotherapy, Phototherapy and Vitamin D

Heliotherapy is defined as medical therapy involving exposure to sunlight. Phototherapy can be defined as the use of medical devices emitting light to treat disease. When heliotherapy was discovered, it was inevitable that light would be used in other disorders to judge its efficacy. This habit persists to the present day with the novel use of new medicines.

In 1905–1907 the Massachusetts General Hospital used "electric light cabinet baths" for patients with eczema, psoriasis and Raynaud's disease (33). In 1915 other uses of the electric light bath were to treat arteriosclerosis, rheumatic and gouty affections, Bright's disease, diabetes, obesity and acute catarrhal affections of the respiratory tract (34). Light was used to treat the wounded of the First World War. It was noted that "even the most serious and extensive wounds will heal much more rapidly" and that "gangrenous, fetid wounds soon become indorous". It was also noted to be an efficient cure for "cases of general exhaustion" (35).

The most enduring use of heliotherapy was the treatment of tuberculosis. At the turn of the century tuberculosis was a common disorder. The pulmonary form would be treated conservatively but extrapulmonary disease would more usually be treated with surgery and came to be known as "surgical" tuberculosis. Unfortunately, radical surgery resulted in disfigurement, and joint and limb diseases in children were commonly treated with this method (36). The alternative treatment of heliotherapy was initiated in 1902. Dr Oskar Bernard, a Swiss physician, treated a knife wound with sunlight after his earlier attempt at surgical repair resulted in the wound dehiscing. The treatment was an unexpected success and he went on to use this technique to treat tuberculosis. He treated open tuberculous cavities and then closed foci of tuberculosis with sunlight locally applied to the affected area. His technique involved gradual lengthening of exposure to sunlight, increasing each day by 10 to 20 minutes to a maximum of three to six hours. Unlike Finsen, he used unfiltered light.

It was another Swiss physician, Dr Auguste Rollier (1874–1954), who cemented the role of heliotherapy as a treatment for all forms of tuberculosis. A friend of Rollier's died following surgical excision of his hip and knee for tuberculosis and then, when Rollier's fiancée developed pulmonary tuberculosis, he gave up his surgical career. He switched to general practice and moved to the town of Leysin. It was here that he developed his sunlight-based treatments for tuberculosis. Rollier advocated the general sunbath rather than the local application of sunlight. His view was that early-morning exposure was of particular value. He combined heliotherapy with rest, fresh air, food and exercise. He would begin treatment with the feet and gradually expose more of the body to the sun, taking on average 15 days to achieve full exposure. Temperature was also important in his treatment regime, as the heat of the sun was to be avoided, with gradual exposure to cold air as it maintained high metabolic activity in patients. During the First World War Rollier also used sunlight to treat intractable war wounds (36).

Heliotherapy was not without its critics. In 1923 *The Lancet* noted that "the results on tuberculosis of the lungs have been, in many hands, disappointing, and have led to avoidance of the treatment by many physicians, and even to its condemnation by some as a dangerous and unjustifiable form of therapy" with unsupervised sunbaths "resulting in a rise of temperature, increased cough, and haemoptysis" (37). In 1932 the Council on Physical Therapy of the American Medical Association published a review on the use of UV therapy in dermatology (38). The review noted, "There is hardly a skin disease or condition for which some physician has not failed to claim good results with ultraviolet radiation". Thirty-four dermatological conditions were listed as disorders in which UV radiation may be useful, and these included acne conglobate, angioma serpiginosum, erysipelas, livedo reticularis, lupus erythematosus, port wine stain, telangiectasia and "ulcers". In a comment to herald future research the review noted that an "undesirable result" of this UV treatment is that it may precipitate attacks of lupus erythematosus. Of the list of disorders published in 1932, the only diseases that continue to be treated with modern phototherapy are eczema, pruritus, psoriasis and scleroderma.

The discovery of vitamin D and its synthesis by UV light is lengthy and complex. A key discovery that light, interacting with the skin, was important in the synthesis of vitamin D occurred in 1925 when Hess and Weinstock fed rachitic rats a small portion of skin from rats that had been irradiated with UV light. It was found that the irradiated skin provided absolute protection from rickets, whereas non-irradiated skin provided no protection, and vitamin D was eventually chemically characterised in 1936 (39).

Niels Finsen's work was translated and led to many publications in the English-speaking medical community, and in the mid-20th century vitamin D started to be used in the treatment of lupus vulgaris and other dermatological conditions in the United Kingdom (UK), Canada, Australia and the United States of America (USA). In 1946 in the UK GB Dowling and EW Prosser Jones published their experience treating lupus vulgaris with oral calciferol (vitamin D_2). Thirty-eight cases were reported. The first case had failed five years of "Finsen applications". He was treated with 50,000 I.U. tds calciferol which was reduced to 50,000 I.U. od over several months. The other patients were treated with similar doses and it was concluded that "the majority, all have appeared to improve, though in a few no very striking change has taken place" (40). These authors also published a similar article in *The Lancet* later that year describing the same patients but also citing the work of the French author Charpy, who published on the same subject, remarkably, during the Second World War, in 1943. Charpy reported 27 cases of "tubercular lupus" with 27 "perfect cures" (translated by Professor R Ramsay, Emeritus Professor of French, The University of Auckland, December 2013) (41, 42). In 1948 Macrae published his experience of the use of oral and injectable calciferol for the treatment of lupus vulgaris (43), reporting good results but suggesting that it was important to get as close as possible to the toxic level and "keep the patient there". He also treated tuberculous lymph nodes, bone and serosal disease. A critical report of the use of calciferol was subsequently published in 1948 (44). In this series of 158 cases of lupus vulgaris the authors emphasised the potential side effects of high-dose calciferol, particularly hypercalcaemia, and were of the opinion that 70% of cases could be cured in 12–18 months by daily UV light baths combined with improved living conditions and diet. The paper also documented the treatment of sarcoidosis, and dermatitis herpetiformis with calciferol. In 1952 Russell reported the use of intralesional calciferol for localised, resistant or recurrent lupus vulgaris. He postulated that the effect of calciferol "is due to the reinforcement of immunologic

processes". The intradermal injections were given at two- to three-week intervals using between 100,000 and 600,000 I.U. Nine cases were described with clinical clearance in six cases. A biopsy on one patient pre- and post-injection showed a smaller infiltrate and more fibrosis (45). The first report of the use of calciferol to treat psoriasis and acne in the UK was by Kindler. "Indurated acne" proved disappointing and most cases were given 50,000 I.U.. to adults and 25,000 I.U. to children. Thirty-one cases of psoriasis were reported, and in 12 the eruption completely or almost completely disappeared (46).

In 1947 Gaumond and Grandbois published the first Canadian case report of the use of oral calciferol in a 33-year-old woman with extensive lupus vulgaris resistant to oral and topical penicillin and UV light. After three and a half months treatment there was a considerable improvement in her skin (47). Gaumond then went on to publish a case series of three patients with lupus vulgaris, all of whom improved significantly with 600,000 I.U. three times per week for the first week, twice weekly for three months and then once weekly for "a period of months" (48). In 1955 Grandbois subsequently published a review of 120 patients with various skin diseases that he had treated with vitamin D_2. Of interest, 24 cases of psoriasis were treated with "excellent" results in five, "good" in six and "nil" in 13. Of seven patients with chronic lupus erythematosus, five were reported with "nil" result. He concluded by noting that:

> The results attained in erythema nodosum, acne pustulosa and conglobata, in lichen planus, in atopic dermatitis and in nummular eczema were very encouraging. Cases of papulonecrotic tuberculid and psoriasis responded in certain instances to vitamin D_2. The drug appears to have no value in the treatment of sarcoidosis, chronic lupus erythematosus, deep mycosis, pustular psoriasis, parapsoriasis and bacterids. (49)

In the southern hemisphere one of the earliest recorded uses of vitamin D_2 was in the treatment of dermatitis herpetiformis and pityriasis rosea, reported in 1958 from Sydney. The patient with dermatitis herpetiformis was noted to have a recurrence in untanned areas that was usefully treated with calciferol. Tanning these areas was also beneficial (50).

There are a greater number of historical publications in the American literature. In 1948, after 13 months of calciferol treatment a 60-year-old woman with a five-year history of endonasal and cutaneous lupus vulgaris was completely healed (51). A case series of the successful treatment of three "negro" patients was reported in 1949 (52). There is one report of the development of "papular necrotic" tuberculid during calciferol therapy. A 53-year-old woman with lupus vulgaris involving the elbow region who was treated with calciferol developed the tuberculid. Calciferol treatment was continued with resultant scarring from the necrotic tuberculid and partial resolution of the lupus vulgaris (53). Several reports are of the use of calciferol in the treatment of parapsoriasis and psoriasis. In 1952 Orlando Canizares reviewed 18 patients, including previously published patients with parapsoriasis. These patients were six women, eight men and four children. Eleven were "cured", four were "failures" and three were "controlled" or 'improved" (54-56). The problem with the term "parapsoriasis" is the definition of disease and within this review parapsoriasis has been split into three groups, including "parapsoriasis guttata", "pityriasis lichenoides et varioliformis acuta" and "parapsoriasis en plaque". It is uncertain how these diseases would be translated into current terminology. In 1951 seven patients with psoriasis were unsuccessfully treated with intramuscular vitamin D_2 (57). A larger review published in 1951 examined a wider variety of cutaneous diseases treated with

calciferol. These diseases included atopic dermatitis, psoriasis, acne conglobate, lupus erythematosus, granuloma annulare and mycosis fungoides. The greatest improvement was with atopic dermatitis and there was no benefit in the one case of granuloma annulare and one case of mycosis fungoides (58). Sawicky in the same year reported the dissemination of granuloma annulare in two patients treated with calciferol (59). In 1954 Bonilla reported three patients who were treated with calciferol for chromoblastomycosis with beneficial effect, and at the time of publication of this case series three other patients were being treated with a combination of calciferol and potassium iodide, as this combination was felt to be more efficacious.

2.2.4 Summary

It is interesting to look back through history to see that the historical definition and classification of disease make it difficult to place historical references in the modern context. The exact time line and methodological processes of moving from light to vitamin D therapy are uncertain. Treatments were based on case reports and case series, which now would be considered poor evidence with the advent of the double-blind, placebo-controlled study adequately powered to detect a difference. The majority of these diseases are now no longer treated with vitamin D. The publications do, however, provide a landscape for modern treatments.

Chapter 3 Vitamin D Physiology, Normal Levels and New Zealand

3.1 Introduction

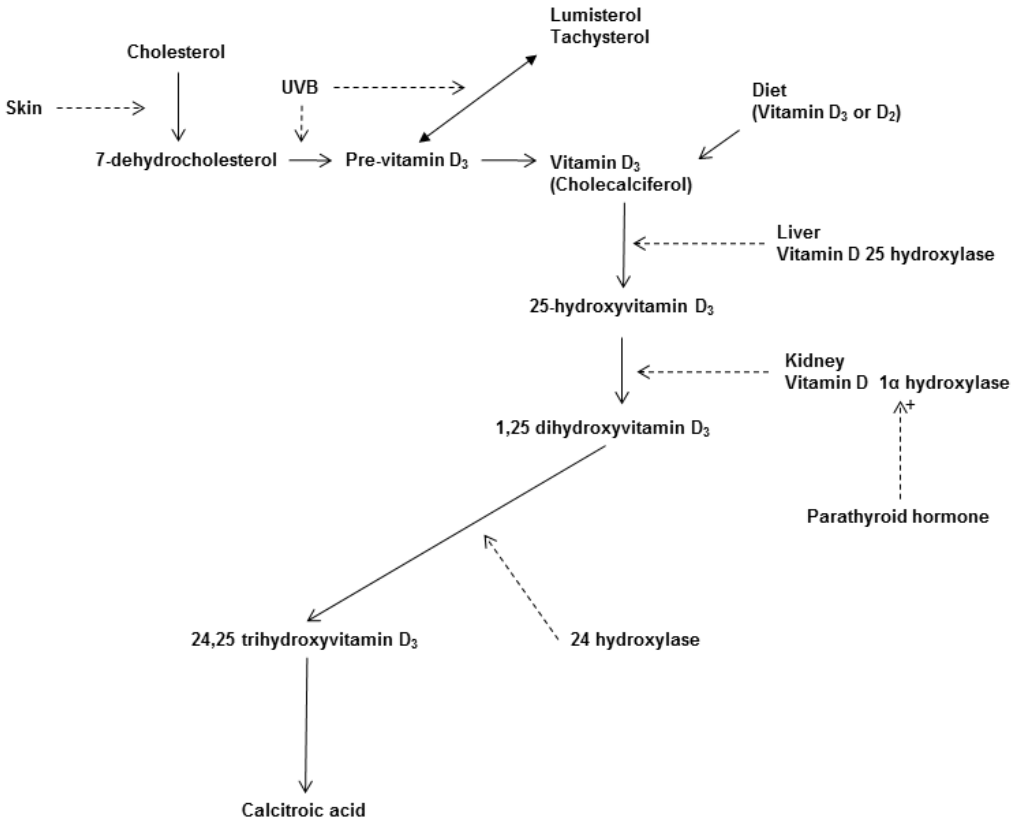
Chapter 3 discusses the current understanding of vitamin D synthesis and metabolism with the controversial subject of normal and abnormal levels of vitamin D, including the New Zealand Ministry of Health consensus statements. It concludes with reported vitamin D levels in New Zealand.

3.1.1 Vitamin D Synthesis and Metabolism

The major source of vitamin D is the skin through sun exposure, which contributes to more than 90% of the serum concentration (60). There are a few naturally occurring sources of vitamin D and these include fatty fish, fish liver oil and egg yolk (60). Some foods can be fortified with vitamin D, including milk, milk products, cereals, formulated beverages, edible oils and margarine. Oral vitamin D supplements are available in New Zealand (61).

The synthesis and degradation of vitamin D is summarised in Figure 1.

Figure 1: Synthesis and degradation of Vitamin D



UVB = Ultraviolet B.

In the skin cholesterol is converted to 7-dehydrocholesterol (7-DHC) by 7-DHC-reductase. 7-DHC is converted to previtamin D_3 by the action of UVB in the skin and the optimum wavelength is 297 nm. Conversion of 7-DHC occurs in the epidermis and dermis. The greatest concentration of 7-DHC is in the

basal and spinous layers of the epidermis (68%), with a significant proportion (26%) in the dermis (62). Immediately after it is formed, previtamin D_3 (precholecalciferol) is converted by non-enzymatic isomerisation to vitamin D_3 (cholecalciferol), which is a temperature-dependent process that occurs over several days. UV radiation also can convert previtamin D_3 to biologically inert lumisterol and tachysterol in a photoreversible reaction, thereby also providing a pool of precursors for the further formation of previtamin D_3. With prolonged sun exposure simulated by a solar simulator in vitro, the continued conversion of previtamin D_3 to lumisterol limits previtamin D_3 accumulation in the skin (63). The concentration of tachysterol remains constant.

With a simulated equatorial location, heavily pigmented skin has a longer time exposure to maximise previtamin D_3 production compared with lightly pigmented skin (63). Furthermore, the time to maximise previtamin D_3 is longer when conditions are simulated at 42^{o} latitude north (Boston, USA) in lightly pigmented skin (63), which is an indication of the effect of latitude on vitamin D synthesis due to the reduction in UV caused by the increase in the zenith angle of the sun (the solar zenith is the angle of the sun away from the vertical); by way of contrast, the latitude of Auckland, New Zealand is 37° south. Changes in skin pigmentation or simulated changes in latitude do not affect the total quantity of previtamin D_3 produced, provided there is sufficient exposure time of the skin. Regardless of skin type, previtamin D_3 reaches a maximum and plateaus at approximately 15% of the original 7-DHC concentration, and further prolonged solar exposure results in a greater quantity of lumisterol in hypopigmented skin than in hyperpigmented skin (64).

The time of year and atmospheric conditions are also important in vitamin D synthesis. UVB is essential for the formation of vitamin D. UVB is scattered and absorbed by oxygen, ozone and atmospheric water. The tilt of the earth's axis through the seasons also alters the intensity of UVB reaching the earth's surface. Therefore, the amount of UVB is variable at different times of the year and at different latitudes. The strongest influence on UVB exposure is latitude, with equatorial latitudes receiving the most annual UVB, peaking at the equinox, and the polar regions receiving almost none (22).

Age decreases the ability of the skin to produce previtamin D_3. There is a twofold reduction in its synthesis among 77- to 82-year-olds compared with 8- to 18-year-olds. There is a steady reduction in 7-DHC in the epidermis (which accounts for 80% of cutaneous production) with age. The age-dependent decrease in the 7-DHC in the stratum basale parallels the age-dependent loss of epidermal mass. The elderly infirm are more likely to be immobile and less likely to expose their skin, potentially compounding this problem (65). The effect of aging on the production of 25-hydroxyvitamin D_3 can be mitigated by pursuing outdoor activities. Data derived from the Third National Health and Nutrition Study showed that those persons aged 60 or more who participated in daily outdoor activities had a mean 25-hydroxyvitamin D level similar to persons aged 20–39 years, with levels of 77 nmol/l versus 79 nmol/l respectively (66).

Sunscreen use suppresses the formation of vitamin D_3, and sunlight itself can cause the photodegradation of vitamin D_3. Para-aminobenzoic acid (a sunscreen) prevents the formation of previtamin D_3 in vitro, and the application of it to the skin of normal volunteers results in a reduction of measureable vitamin D after UV irradiation (67). Furthermore, non-protected human skin exposed to summer noon sunlight at 42.2° north showed 80% loss of the vitamin D_3 after three hours of exposure. This loss can be demonstrated at all

times of year after exposure to sunlight at this latitude, including the winter, when there is insufficient UV to convert 7-DHC to previtamin D_3 (68).

Vitamin D_3 is transported to the liver bound to VDBP, where it is hydroxylated at C-25 to 25-hydroxyvitamin D_3 by one or more cytochrome P450 vitamin D 25-hydroxylases, including CYP2RI (a key enzyme) and CYP2D11 and CYP2D25 (69). 25-hydroxyvitamin D_3 is then transported to the kidneys bound to VDBP and filtered through the glomerulus (69). The complex is then reabsorbed in the proximal tubules by an endocytic process involving the binding of the complex to megalin (70). Megalin is a receptor expressed in the proximal tubules and is a member of the low-density lipoprotein receptor superfamily mediating the uptake and lysosomal degradation of numerous macromolecules (71). 25-hydroxyvitamin D_3 is hydroxylated at the C-1 position to form the biologically active form of vitamin D 1, 25-dihydroxyvitamin D_3. The enzyme that converts 25-hydroxyvitamin D_3 to 1, 25-dihydroxyvitamin D_3, is a cytochrome P450 enzyme 1α hydroxylase and is found predominately in the kidney. 1α hydroxylase is also found in extrarenal sites, including macrophages, basal keratinocytes, hair follicles, lymph nodes, colon, pancreas, adrenal medulla, cerebellum, cerebral cortex and placenta (72).

In the kidneys the conversion of 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3 is tightly controlled by parathyroid hormone (PTH), calcium, phosphate, calcitonin, fibroblast growth factor 23 (FGF23) and 1,25-dihydroxyvitamin D_3 itself. FGF23 promotes renal phosphate excretion by decreasing its absorption in the proximal tubule. Calcitonin can stimulate 1, 25-dihydroxyvitamin D_3 production and this may be important during pregnancy. 24-hydroxylase converts 25-hydroxyvitamin D_3 to 24, 25-dihydroxyvitamin D_3, a relatively inactive metabolite that can subsequently be oxidised. However, its main function is to metabolise 1, 25-dihydroxyvitamin D_3 to 1, 24, 25-trihydroxyvitamin D_3, which then undergoes oxidation, side chain cleavage and then excretion as calcitroic acid (69).

3.1.2 Vitamin D Receptor and Genomic Regulation

The vitamin D receptor (VDR) for 1, 25-dihydroxyvitamin D_3 is distributed in many tissues (73). The VDR is a member of the superfamily of nuclear receptors and exerts a slow effect (over hours or days) in the nucleus when bound to its ligand (74). When 1, 25-dihydroxyvitamin D_3 binds to the VDR, the VDR interacts with the retinoid X receptor to form a heterodimer. This complex then binds to vitamin D responsive elements (VDRE) on promoter regions of genes directly controlled by 1, 25-dihydroxyvitamin D_3. Coactivators or corepressors are also recruited to modulate the transcription of genes, which encode proteins that carry out the functions of vitamin D (73).

The traditional genomic effects are regulation of bone metabolism, calcium and phosphate balance. Genes that are modulated directly by 1, 25-dihydroxyvitamin D_3 include mRANKL (bone resorption), MLRP5 (bone anabolism), hTRPV6 (intestinal calcium transport) and hFGF23 (renal phosphate resorption). In addition to these genes, non-traditional genes directly modulated by 1, 25-dihydroxyvitamin D_3 include hCYP24A1 (1, 25-dihydroxyvitamin D_3 detoxification), hp21 and hFOXO1 (cell cycle control) and hCAMP (antimicrobial peptide) (73).

1, 25-dihydroxyvitamin D_3 can also stimulate rapid responses (within minutes to hours) that include calcium uptake from the intestine (75), augmentation of insulin release from pancreatic β cells (76), vascular smooth

muscle migration (77) and DNA synthesis in keratinocytes (78). These rapid non-genomic responses are mediated by membrane-bound VDR present in caveolae, and confocal microscopy shows the VDR is in close association with the caveolae proteins (74). Caveolae are cup-shaped membrane pits, 60–80 nm in diameter, composed of cavin proteins and rich in sphingolipids at the neck and base of the membrane cup (79).

Therefore, vitamin D is a hormone involved in many physiological processes, including metabolism control, cell growth regulation and immune functions.

3.1.3 Normal Vitamin D Levels

In clinical measurement, vitamin D levels are assessed by the measurement of 25-hydroxyvitamin D rather than 1, 25-dihydroxyvitamin D. The half-life of 1, 25-dihydroxyvitamin D is four to six hours, whereas that of 25-hydroxyvitamin D is two to three weeks. 1, 25-dihydroxyvitamin D circulating levels are a thousand-fold less than those of 25-hydroxyvitamin D. When a patient becomes vitamin D deficient, the action of PTH increases the renal production of 1, 25-dihydroxyvitamin D, resulting in normal or elevated levels (80).

Patient samples may contain both 25-hydroxyvitamin D_3 (cholecalciferol) and exogenous dietary-derived 25-hydroxyvitamin D_2 (ergocalciferol). Most routine assays do not differentiate between the two forms (or other smaller quantities of cross-reactants) and therefore 25-hydroxyvitamin D is reported (81). There are different laboratory techniques to measure vitamin D levels and they can be grouped into two categories: immunoassay based or chromatography based. Chromatography is considered the gold standard. However, this technique requires considerable expertise, especially with calibration, and is expensive. Immunoassay techniques are in widespread use, as they can be automated and have a quick turnaround time. However, this technique faces problems of selectivity, cross-reactivity and accuracy (81). A recent expert panel convened in the UK concluded that chromatography methods were to be preferred for the UK National Diet and Nutrition Survey (82).

Debate has surrounded the definition of the normal and abnormal range of vitamin D and consensus is difficult to achieve. Studies of normal physiology and vitamin D levels can help to establish the normal range. Mathematical modelling of 25-hydroxyvitamin D against PTH levels can demonstrate a plateau effect at 80 nmol/l, suggesting this is a physiologically normal level (83). However, a study of 312,962 patients found no threshold above which increasing vitamin D levels failed to suppress PTH in a 25-hydroxyvitamin D range of approximately 190 to 25 nmol/l (84). In contrast, in a study of 19,172 patients a 25-hydroxyvitamin D level greater than 75 nmol/l did not seem to be associated with additional change in PTH (85).

25-hydroxyvitamin D levels beginning at 75 nmol/l and with an optimum between 90 and 100 nmol/l give the most advantageous outcome for muscular function, periodontal disease, risk of falls and fractures, and colorectal cancer (86). A dose-response relationship exists between 25-hydroxyvitamin D levels and FEV_1 in a US population when adjustment is made for age, gender, smoking, ethnicity and height. The FEV_1 is a measure of how much air a person can exhale in the first second of the forced breath. The mean FEV_1 was greater for the highest quintile of 25-hydroxyvitamin D (≥85.7 nmol/l) compared with the lowest quintile (≤40.4 nmol/l; $p < 0.0001$) (87). Furthermore, in this same population 25-hydroxyvitamin D levels were

inversely associated with systolic blood pressure after adjustment for age, sex, ethnicity, physical activity and body mass index (BMI). Systolic blood pressure was 3.0 mmHg lower for those in the highest quintile (≥85.7 nmol/l) compared with the lowest (≤40.4 nmol/l) (88). One consensus view of the minimum desirable 25-hydroxyvitamin D level clustered between 70 and 80 nmol/l (89).

The 2012 New Zealand Ministry of Health Consensus Statement on Vitamin D and Sun Exposure considers an optimal level of vitamin D (25-hydroxyvitamin D) to be 50 nmol/l or over and deficiency to be below 25 nmol/l (90). The 2012 New Zealand Ministry of Health report on the vitamin D status of New Zealand adults, acknowledging the consensus statement, uses the definitions of high, recommended, deficient and mild, moderate or severe deficiency summarised in Table 1 (91). These definitions were adopted for the purposes of the clinical studies of this thesis.

Table 1: New Zealand Ministry of Health definitions of vitamin D (25-hydroxyvitamin D) status (91)

Definition	Serum level (nmol/l)
High level	≥125
Equal to or above the recommended level	≥50
Below recommended level but not deficient	49.9–25.0
Vitamin D deficiency	<25.0
Mild to moderate deficiency	24.9–12.5
Severe deficiency	<12.5

3.1.3.1 Vitamin D Levels in New Zealand

In a national sample of 2,946 New Zealanders in 1997 aged 15 years and over the average 25-hydroxyvitamin D_3 levels were 47 nmol/l in women and 52 nmol/l in men. This study, published in 2006, used definitions of deficiency and insufficiency that differ from those currently used by the New Zealand Ministry of Health. 25-hydroxyvitamin D levels were measured by the immunoassay technique. There was a 3% prevalence of 25-hydroxyvitamin D deficiency (≤17.5 nmol/l) and an 84% prevalence of insufficiency (≤ 80 nmol/l). Mean concentrations in New Zealand European and others were 51 nmol/l, in Māori 42 nmol/l and in Pacific peoples 37 nmol/l. Compared with the most recent study, 2008/09, the 1997 study showed that 25-hydroxyvitamin D levels in women declined with age. Seasonal differences were 31 nmol/l in women and 28 nmol/l in men, and obese women had lower levels than non-obese women. Women in South Island had a mean 25-hydroxyvitamin D level 6 nmol/l lower than those in North Island. Ethnicity and season were the main determinants of 25-hydroxyvitamin D in New Zealanders (92).

In 2008/09 the majority of New Zealand adults (68.1%) had levels of 25-hydroxyvitamin D equal or above 50 nmol/l. However, 4.9% of adults had 25-hydroxyvitamin D deficiency and 0.2% of adults had severe deficiency. In contrast to the 1997 study, 25-hydroxyvitamin D levels were measured by chromatography methods. The average overall mean for New Zealand adults was 63.0 nmol/l. Differences in population groups were noted. Pacific people were 2.3 times more likely to have 25-hydroxyvitamin D deficiency than non-Pacific adults, adjusting for age. Socioeconomic factors are important, with people living in the most deprived areas having lower 25-hydroxyvitamin D levels (56.6 nmol/l) compared with those in the least deprived areas (69.9 nmol/l). About 7% of those living in the most deprived areas were 25-hydroxyvitamin D deficient compared with 3% in the least deprived areas. The obese (BMI > 30 kg/m^2) had a lower mean

level of vitamin D (57.0 nmol/l) than those in the normal (BMI = 18.5–24.9 kg/m^2) or underweight (BMI < 18.5 kg/m^2) range, whose average was 66.3 nmol/l. Latitude and season affect 25-hydroxyvitamin D levels, with deficiency being more likely in late winter and spring. This was noted particularly in South Island, south of Nelson Marlborough District Health Board. The prevalence of 25-hydroxyvitamin D deficiency did not vary by age group, and 4.3% of men and 5.4% of women were 25-hydroxyvitamin D deficient (91).

In summer (February), 88% of a volunteer group in Christchurch had a 25-hydroxyvitamin D level < 75 nmol/l, which rose to 100% in winter (June and July). While ethnicity was not determined in the volunteer group, 25-hydroxyvitamin D levels closely followed UVB irradiation (93). Using 25-hydroxyvitamin D levels from 21,987 adults collected over 10 months from 1 January until September 30 in Auckland, seasonal variation was established in differing ethnic groups. Peak levels of 25-hydroxyvitamin D occurred in summer (February) and the trough was in winter (August). While there was no significant difference between ethnic groups in the amount of seasonal variation, there were significant differences between ethnic groups. New Zealand Europeans had higher levels than Māori, Polynesian and Southeast/East Asian descent. Indian, Middle Eastern and African ethnicities had the lowest levels (94).

In Auckland and Dunedin 502 volunteers wore personal dosimeters on their wrists for 8 weeks during daylight hours (95). Additionally, clothing diaries enabled calculation of skin coverage. This study demonstrated that vitamin D status was increased by regular small sun exposures of less than two standard erythemal doses (corrected for clothing) per week and that greater exposures resulted in only small additional increases in 25-hydroxyvitamin D levels. Furthermore, there was no difference in the association between UV exposure and 25-hydroxyvitamin D between ethnic groups.

In clinical settings in New Zealand, levels of 25-hydroxyvitamin D below those recommended have been demonstrated in several small descriptive studies. In pregnant women, in a general practice setting in Wellington, 90% of Māori (9 of 10) and 95% of Pacific women (20 of 21) were below 50 nmol/l, but in the European group 67% (8 of 12) were below the recommended level (96). In rheumatology clinics in Wellington and Wanganui 78% (43 of 55) had 25-hydroxyvitamin D levels less than 50 nmol/l. This study did not define ethnicity and the majority of patients had rheumatoid arthritis (97). In an ear, nose and throat clinic in South Auckland 58% (28 of 48) had 25-hydroxyvitamin D levels below 50 nmol/l. The ethnicities were described in this study. Within the ethnic groups those with 25-hydroxyvitamin D levels below 50 nmol/l were European 46% (6 of 15), Māori 67% (8 of 12), Pacific 88% (7 of 8) and Southeast Asian 54% (5 of 11). The study analysed those with 25-hydroxyvitamin D levels less than 50 nmol/l against Fitzpatrick skin type, and a correlation ($p < 0.05$) was noted between lower levels of 25-hydroxyvitamin D and darker skin colour (98). Fitzpatrick skin typing is an accepted classification of skin type depending on response to sunlight, and in this study, type I skin was defined as very white, always burns, never tans and type VI as black, never burns, tans profusely.

Overall, these studies indicate that most New Zealanders, especially European New Zealanders, have sufficient 25-hydroxyvitamin D, although New Zealanders of coloured skin are at risk of 25-hydroxyvitamin D inadequacy and these ethnic groups include Māori, Pacific, Indian and Asian. Latitude, seasonal variation and socioeconomic status are also important factors.

Chapter 4 Literature Review

There are large numbers of publications related to vitamin D and the skin. This review examines the width of the literature but focuses in depth on those publications related to cutaneous lupus and then psoriasis. Specifically, the literature examining the prevalence of cutaneous lupus and the role of vitamin D in cutaneous lupus and psoriasis is reviewed because these two diseases are the specific areas of research relevant to the thesis (see Chapters 5 and 6). The literature search strategies are described in Appendix 1.

Then, for completeness of the thesis, other dermatological diseases that have relevance to vitamin D are briefly reviewed. These are atopic dermatitis, skin cancer and sun-seeking behaviour, vitiligo and albinism, systemic sclerosis, Behçet's disease and miscellaneous skin diseases.

As the topic of antimicrobial peptides and vitamin D intersects with a number of relevant skin diseases, this forms a separate section.

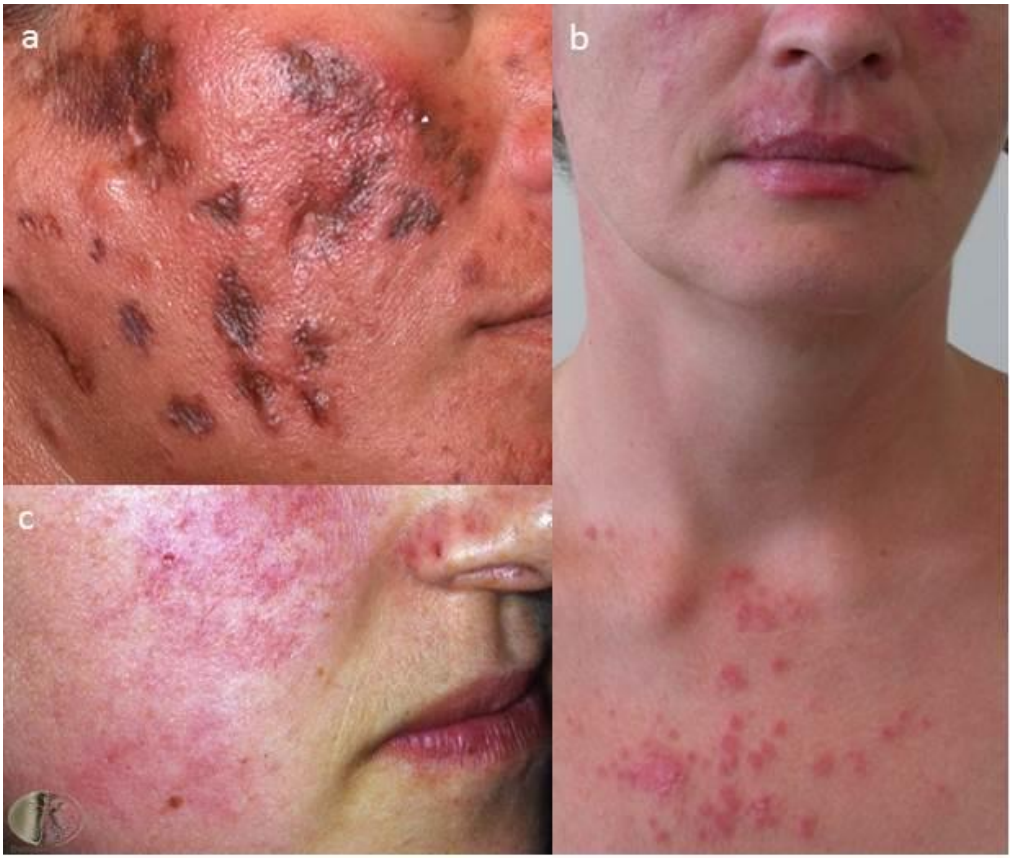
The final section reviews the relevant literature about the relationship between cardiovascular disease and psoriasis, including lifestyle, as this forms the final study of the thesis (see Chapter 7).

4.1 Cutaneous Lupus

Systemic lupus erythematosus (SLE) is a systemic, chronic inflammatory autoimmune disease that can be definitely diagnosed when four or more diagnostic criteria are present, either simultaneously or serially, based on the American Rheumatism Association 1982 revised criteria (99). The cutaneous criteria are malar rash, discoid rash and photosensitivity, based on clinical appearances and not histology. The malar rash is defined as "fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial fold". The discoid rash is defined as "erythematous raised patches with adherent scaling and follicular plugging; atrophic scarring may occur in older lesions". Photosensitivity is defined as "skin rash as a result of unusual reaction to sunlight, by patient history or physician observation". The other diagnostic criteria are oral ulcers (oral or nasopharyngeal, usually painless, observed by a physician), arthritis (nonerosive involving two or more peripheral joints), serositis (pleuritic or pericarditis), renal disorder (proteinuria or cellular casts), neurological disorder (seizures or psychosis), haematological disorder (haemolytic anaemia, leukopaenia, lymphopaenia or thrombocytopaenia), immunological disorder (positive lupus erythematosus cell preparation, anti-DNA antibody, anti-Smith antibody or false positive serological test for syphilis) or antinuclear antibody (in the absence of drugs known to be associated with drug-induced lupus).

A classification of cutaneous lupus, irrespective of systemic involvement, was described in 1981 (100).This classification divided cutaneous lupus into three groups: chronic cutaneous lupus erythematosus or discoid lupus (DLE), subacute cutaneous lupus (SCLE) and acute cutaneous lupus (ACLE). DLE is further split into localised (above the neck) or generalised (lesions above and below the neck) and hypertropic DLE. The European Society of Cutaneous Lupus Erythematosus uses a similar classification of ACLE, SCLE and chronic cutaneous lupus, which is further subdivided into DLE, lupus panniculitis and chilblain lupus. Intermittent (tumid) lupus is regarded as a separate category (101). An illustration of the different types of lupus is shown in Figure 2.

Figure 2: Types of cutaneous lupus



a) Discoid lupus erythematosus. b) Subacute cutaneous lupus. c) Acute cutaneous lupus in the setting of systemic lupus erythematosus. (a & b personal collection, c reproduced with permission from DermNet NZ.)

The clinical and laboratory features of DLE are localised chronic scarring lesions, lasting months or years and usually with no extra-cutaneous involvement. Antinuclear antibodies are occasionally positive in low titre, and anti-double stranded DNA (anti-dsDNA) is also occasionally present in low titres. SCLE is either papulosquamous or annular-polycyclic, and clinically usually consists of widespread non-scarring lesions with scale, depigmentation and telangectases in a photodistributed pattern lasting weeks to months. It is associated with systemic disease but severe renal or central nervous system disease is uncommon. Antinuclear antibody (ANA) is usually positive and anti-dsDNA is present in low concentration. SCLE patients also frequently have antibodies to the extractable nuclear antigens Ro and La. Auto antibodies to nuclear antigens are associated with different connective tissue diseases, and anti Ro and anti La were named after the first two letters of the surnames of the patients in whom they were first found. ACLE can be localised and indurated, just over the malar face, or widespread to include scalp, neck, trunk, arms and hands lasting hours to days. ANA is usually present, along with anti-dsDNA, which is usually present in high concentrations. The broad histological features of these three groups overlap and variably include hyperkeratosis, epidermal atrophy, follicular dilatation with keratin plugging, liquefactive degeneration at the dermo-epidermal junction, basement membrane thickening and a superficial and deep perivascular infiltrate (102). Table 2 is a summary of the clinical features and serology of the common types of cutaneous lupus.

Table 2: Summary of the common types of cutaneous lupus, clinical features and serology

Type of lupus	Clinical site/type of involvement			Serology		
	Face	Body (not face)	Scarring	ANA	Ds-DNA	Ro
DLE	√	X	√	−	−	−
SCLE	√	√/X	X	+	+ (low concentration)	+
ACLE	√	√/X	X	+	+	+

√ = Usually present, X = Usually absent, √/X = Variable, + = Usually present, − = Usually absent. DLE = Discoid lupus, SCLE = Subacute cutaneous lupus, ACLE = Acute cutaneous lupus erythematosus. ANA = antinuclear antibody, Ds-DNA = Double stranded deoxyribonucleic acid.

Rarer forms of cutaneous lupus have subsequently been recognised and these have been integrated into the original classification. These include toxic epidermal necrolysis-like ACLE into the ACLE group, mixed pattern into the SCLE group and mucosal, tumid, chilblain and DLE-lichen planus overlap into the DLE group (103). Many drugs are also recognised to induce lupus, and antihistone antibodies may be detected. The groups of drugs include antiarrhythmic, antihypertensive, antidepressant, antipsychotic, antibacterial and anti-inflammatory (104).

There are many different treatments for cutaneous lupus. Advice about sun avoidance and sunscreen is usual. Topical treatments are potent or ultrapotent steroids, such as betamethasone valerate or clobetasol propionate, calcineurin inhibitors and topical retinoids. Systemic treatments include hydroxychloroquine, prednisone, methotrexate, retinoids (acitretin or isotretinoin), thalidomide, dapsone and clofazimine (1).

4.1.1 The Prevalence and Incidence of Cutaneous Lupus

The prevalence and incidence of cutaneous lupus in New Zealand is not known. Only three population-based studies have been published internationally on the prevalence and incidence of cutaneous lupus. Furthermore, there is little published evidence examining the rates of systemic lupus among Pacific people and Māori, and there is no published evidence about cutaneous lupus in Pacific people and Māori.

Two studies have described the prevalence of systemic, rather than cutaneous, lupus erythematosus in Pacific people and Māori (105, 106). Three have specifically examined cutaneous lupus prevalence and incidence (107-109) in Europe and America. Danchenko et al published a summary of incidence and prevalence of SLE around the world, which examined different racial groups (110). These studies are summarised in Table 3.

Table 3: Summary of prevalence and incidence of SLE and cutaneous lupus

Author	Type of lupus	Data source	Patient numbers Male/female	Location	Prevalence (per 100,000)	Incidence (per 100,000 person-years)
Serdula 1979 (105)	SLE	Hospital discharge	n = 168 Male 13 Female 155	Hawaii, USA	White 5.8 Part-Hawaiian 20.4	Not given
Hart 1983 (106)	SLE	Hospital discharge	n = 136 Male 13 Female 123	Auckland, NZ	White 14.6 Polynesian* 50.63	Not given
Danchenko (110)	SLE	Electronic resource Medical journals	N/A	N/A	UK Afro-Caribbean 159.4 White 20.5 USA Black 19.5 White 7.4	45.6 (Range 7.4–159.4)**
Popovic 2007 (107)	SCLE	Immunology laboratory	n = 59 Male 9 Female 50	Stockholm County, Sweden	6.2–14	0.7
Durosaro 2009 (108)	DLE,SCLE, Lupus panniculitis, Bullous lupus	Hospital and community	n = 156 Male 56 Female 100	Olmsted County, Minnesota, USA	73.24	4.3
Deligny 2010 (109)	DLE, panniculitis, tumid	Hospital and community	n = 20 Male 2 Female 18	French Guiana, South America	Not given	2.59

* Polynesian = Māori, Pacific Islander, mixed blood. SLE = Systemic lupus erythematosus, DLE = Discoid lupus erythematosus, SCLE = subacute cutaneous lupus. ** Mean of 23 studies.

The first report on the frequency of SLE in a Pacific population was published in 1979 by Serdula et al (105). In Hawaii, the prevalence of SLE in the “part-Hawaiian” community was 20.4, compared with 5.8 per 100,000 in the “white” population. This study looked at hospital records, rather than the community, on the Hawaiian island of Oahu between 1970 and 1975. The denominator was the 1975 government population estimates. A total of 168 patients with SLE were identified, of whom 107 were considered to have definite SLE and 155 (92%) were women. The age-adjusted prevalence of the definite cases was Chinese 24.1, part-Hawaiian 20.4, Filipino 19.9, Japanese 18.2 and white 5.8 per 100,000.

In 1983 Hart published a retrospective study to determine the ethnic differences in the prevalence of SLE in Auckland (106). Patients were identified by examining hospital records between 1975 and 1981, and ethnic groups were identified by self-declared national census and hospital record data. The national death register was checked to exclude unrecorded deaths and the denominator was the population estimates for Auckland taken from the 1976 census. A total of 136 patients were identified with SLE, of whom 106 were considered to have definite SLE and 123 were women (90%). In all age groups the prevalence was higher in Pacific people and Māori. The age-adjusted prevalence for Māori and Pacific people was 50.6 compared

with the European prevalence of 14.6 per 100,000, which is a significant difference ($p < 0.001$). The prevalence of the "other" group, which consisted of mainly Chinese and Indian, was 19.11 per 100,000, although overall numbers in this group were low (n = 6). This study did not identify patients with SLE in the community who had not been referred to the hospital, and would have missed mild cases and those cared for solely in the private sector. The cause of the higher prevalence of SLE in Māori and Pacific people is not known. In Auckland the age-specific mortality rate was 13.0 in Māori and Pacific people compared with 2.5 per million person-years in white people, and in Hawaii the mortality rate was 14.46 in non-white compared with 1.89 per million person-years in white people.

A Swedish study examined the incidence and prevalence of Ro positive SCLE in Stockholm County, and the prevalence was estimated to be 6.2–14 per 100,000 and the incidence 0.7 per 100,000 person-years (107). The study identified 1,323 patients from three immunology laboratories who tested positive for Ro antibodies from Stockholm County during 1996–2002. The patients still living in the county were identified, and ultimately 125 were examined clinically. The primary reasons for the Ro testing were not given. Of the 125 examined, 59 were confirmed as having lupus erythematosus and SCLE was found in 20, DLE in 6 and systemic lupus in 33. The ethnicity was not recorded in this study; however, the population of this county is mostly Caucasian (personal communication from Professor Fillipa Nyberg, Karolinska Institute, Stockholm, Sweden).

A population study from Olmsted County, Minnesota, USA, reported an age- and sex-adjusted prevalence of cutaneous lupus at 1 January 2006 of 73.24 (95% CI: 58.29–88.19) per 100,000 (108). The study used data obtained from all inpatient and outpatient records of the residents of Olmsted County with medical diagnoses that were made at various health care facilities, including clinics, hospitals, nursing homes and post-mortems between 1965 and 2000. The paper does not state, however, whether every health care facility was included. A total of 156 patients with cutaneous lupus were identified and 100 were female. The results are summarised in Table 4.

Table 4: Summary of cutaneous lupus in Olmsted County (108)

Type of cutaneous lupus	**Numbers (%) n = 156**	**Incidence (age- and sex-adjusted per 100,000 person-years)**
DLE	129 (82.7)	3.56
SCLE	23 (14.7)	0.63
Panniculitis	3 (1.9)	0.07
Bullous	1 (0.7)	0.03

DLE = Discoid lupus, SCLE = Subacute cutaneous lupus.

A population-based study from French Guiana used multiple sources to find cases of lupus from dermatology, rheumatology and internal medicine, both public and private. The incidence rates for chronic cutaneous lupus were derived from 18 cases of DLE, one of lupus panniculitis and one of tumid lupus. Although the denominator data were not reported, the crude average incidence was 2.59 per 100,000 (95% CI: 1.5–4) for the period 1 January 1995 to 31 December 1999, and for definite cases, was more common in women than men, with incidence rates of 3.4 (95% CI: 1.8–5.8) and 0.5 (95% CI: 0.06–1.9) per 100,000 respectively (109).

A study in 2006 examined the prevalence of SLE in white and non-white groups in different countries around the world (110). In the UK the prevalence was 159.4 in the Afro-Caribbean community compared with 20.5 per 100,000 in the white community. In the USA the prevalence was 19.5 in the black population compared with 7.4 per 100,000 in the white.

In summary, lupus is an uncommon disease in the community. The most common types of cutaneous lupus are discoid, subacute cutaneous and that associated with systemic lupus. Other subtypes, including panniculitic, bullous, tumid and drug-induced are less common. People of coloured skin and females have a greater risk of developing lupus compared with those of less colour and males. However, cutaneous lupus can affect many different racial groups.

4.1.2 Cutaneous Lupus and Vitamin D

This section reviews the literature about cutaneous lupus and vitamin D. It also discusses the cellular and molecular mechanisms of cutaneous lupus. It concludes with a section on Ro antigen and its homologs.

4.1.2.1 Clinical Studies

Cutaneous lupus can be induced by both UVA and UVB radiation. In a study to determine the role of UV exposure in inducing cutaneous lupus, 128 patients with cutaneous lupus were tested with UVA and UVB on two separate, uninvolved sites on the back or extensor surface of the arm. Eleven of 36 patients with DLE reacted to UVB alone and 20 reacted to UVA and UVB. Six of 14 patients with SCLE reacted to UVB alone and six reacted to both UVA and UVB given at separate sites. One of five patients with SLE reacted to UVB alone and three reacted to both UVA and UVB given at separate sites. The provoked lesions had a latency of two weeks and persisted for several weeks to months (111).

In the clinical management of patients with cutaneous lupus it is accepted practice to advise against excessive sun exposure to limit provocation of cutaneous lupus. Advice includes wearing of suitable clothing and hats, and the liberal application of sunblock. Sunblock protects against UV-induced cutaneous lupus. A double-blind, within-person comparative study of 11 patients with cutaneous lupus, who had their lupus provoked by UVA and if needed by the addition of UVB, demonstrated that sunblock can provide strong protection against induced lesions and that different sunblocks provide differing levels of protection (112). In a larger retrospective study of 51 patients with cutaneous lupus provoked by UVA or UVB or UVA and UVB, 49 (96%) were entirely protected by sunblock against the development of cutaneous lupus (113).

Studies examining vitamin D status in patients with cutaneous lupus are summarised in Table 5. An uncontrolled study from Ireland measured the 25-hydroxyvitamin D levels of 52 patients with biopsy-proven cutaneous lupus and found an overall mean (SD) of 63.0 (± 23.3) nmol/l, and two patients (3.8%) were found to have levels < 25 nmol/l. The levels were significantly lower among sun avoiders who were defined by use of photoprotective clothing/limitation of outdoor exposure “frequently or always” compared with those who did not. Mean (SD) 25-hydroxyvitamin D levels were 58.3 (± 20.7) nmol/l and 81.8 (± 29.3) nmol/l respectively, p = 0.004. Additionally, daily sunblock users who were defined by the daily sunscreen application all year round had lower mean 25-hydroxyvitamin D levels compared with those who did not, 57.9 (± 22.2) nmol/l and 73.5 (± 26.7) nmol/l respectively, p = 0.042. Furthermore, higher mean 25-hydroxyvitamin D levels were found in those who took vitamin D supplementation, a minimum of 400 IU/day

of cholecalciferol, than those who did not, 74.6 (± 26.5) nmol/l and 57.5 (± 22.5) nmol/l respectively, p = 0.015 (114).

Another case series from Hannover, Germany, measured the levels of 25-hydroxyvitamin D_2 (note not 25-hydroxyvitamin D_3) in 14 patients with DLE and 13 patients with SCLE (115). Defining less than 50 nmol/l as deficient, and 50–75 nmol/l as insufficient, one patient with SCLE and four with DLE were insufficient, while 11 patients with SCLE and nine patients with DLE were insufficient. The seasonal timing of the study was not stated.

A larger case-control study from Berlin, Germany, of 41 patients with DLE or SCLE, demonstrated vitamin D deficiency (defined as 25-hydroxyvitamin D < 50 nmol/l) throughout the year (116). In the lupus group vitamin D deficiency was noted in both summer and winter. There was a reported difference between the lupus group and healthy controls in summer and winter ($p \leq 0.0001$); however, the absolute values with confidence intervals were not reported.

In a case-control study from Spain, 55 patients with cutaneous lupus were compared with 37 healthy age- and sex-matched controls (117). This study reported that 95% of patients with cutaneous lupus had a 25-hydroxyvitamin D level of less than 75 nmol/l, which was defined by the authors as the lower limit for vitamin D “adequacy”. Mean (SD) 25-hydroxyvitamin D levels were significantly lower in cases, 49.9 (± 22.2) nmol/l than in controls 59.4 (± 18.7) nmol/l, p = 0.038. A history of cutaneous lupus was a strong predictor of insufficiency of 25-hydroxyvitamin D (OR 4.2; 95% CI: 1.0–17.4). It is interesting to note that using these authors’ definition of 25-hydroxyvitamin D “adequacy”, the control group were not “adequate” by the New Zealand Ministry of Health guidelines but were “equal [to] or above the recommended level”.

A case-control study from Dallas, USA, matched 25 African-American patients with cutaneous lupus and 26 healthy African-Americans by age, sex and season. The findings were contrasted to a similar comparison of 26 Caucasian and Hispanic patients with cutaneous lupus, and 24 Caucasian and Hispanic healthy controls matched by age, sex and season. (118). Almost half the African-American subjects in both the lupus and control groups were vitamin D insufficient (less than 50 nmol/l). There was no significant difference in 25-hydroxyvitamin D mean (SD) levels between cases and controls among the African- American group at 52.0 (± 18.5) nmol/l and 54.8 (± 21.2) nmol/l, p = 0.62 respectively; or the Hispanic group at 59.4 (± 21.0) nmol/l and 70.5 (± 27.4) nmol/l, p = 0.12. Two-way analysis of variance (ANOVA) demonstrated that African-American patients, compared with Caucasian/Hispanic with cutaneous lupus, had significantly lower mean levels of 25-hydroxyvitamin D (52.0 nmol/l and 59.4 nmol/l respectively, p = 0.008). However, controlled for skin colour, patients with cutaneous lupus were not found to have significantly different levels of 25-hydroxyvitamin D_3 (p = 0.13).

Table 5: Vitamin D deficiency in cutaneous lupus

Author	Study type & country	Patient source, numbers and lupus type	Sex/age (years)	25-hydroxyvitamin D levels (% deficiency-defined by study)
Cusack 2008 (114)	Cross-sectional case series Ireland	Hospital outpatients n = 52 Type not reported	Male n = 5 Female n = 47 Median age 43	Deficient 3.8 (< 25 nmol/l) Overall mean 63.02 ± 23.3 nmol/l
Renne 2008 (115)	Cross-sectional case series Germany	Hospital outpatients n = 27 (DLE n = 14,SCLE n = 13)	Not reported	*Deficient 74.1 (< 50 nmol/l) Insufficient 18.5 (50–75 nmol/l)
Heine 2010 (116)	Case control Germany	Hospital outpatients n = 41 (25 healthy controls, 24 "Allergy" controls, 1,951 "reference" pool) (DLE n = 10,SCLE n = 31)	Not reported	Deficient Summer 85.7 Winter 97.1 (< 50 nmol/l) *absolute values not given
Cutillas-Marco 2010 (117)	Case control Spain	Hospital outpatients n = 55 (37 controls) (DLE n = 44,SCLE n = 11)	Males n = 13 Median age 49.7 Females n = 42 Median age 46.9	Insufficient 83.6 (25–75 nmol/) Deficient 10.9 (> 25 nmol/l) Cases mean 49.9 ± 22.2 nmol/l Controls mean 59.4 ± 18.7 nmol/l (p = 0.03 controlled for age)
Word 2011 (118)	Case control USA	Hospital outpatients n = 25 (26 controls) African-American (DLE n = 20,SCLE n = 2, ACLE n = 3) n = 26 (24 controls) Hispanic & Cauc DLE n = 13, SCLE n = 8, ACLE n = 3, other n = 2)	African-American Mean age 42 Males n = 2 Females n = 23 Hispanic & Cauc Mean age 48.2 Males n = 1 Females n = 25	Insufficient 48 African-American 38 Hispanic & Cauc (< 50 nmol/l) African-American cases 52.0 ± 18.5 nmol/l African-American controls 54.8 ± 21.2 nmol/l (p = 0.62) Caucasian/Hispanic cases 59.4 ± 21.0 nmol/l Caucasian/Hispanic control 70.5 ± 27.4 nmol/l (p = 0.12)

DLE = Discoid lupus, SCLE = Subacute cutaneous lupus, ACLE = Acute cutaneous lupus. Cauc = Caucasian. * Measured 25-hydroxyvitamin D_2.

In summary, cutaneous lupus is an uncommon disease and it is difficult for a single centre to undertake a sufficiently large study to obtain meaningful results. The studies of cutaneous lupus and 25-hydroxyvitamin D suffer from small numbers and design limitations. A type 2 error is possible. The variability of the definition of 25-hydroxyvitamin D deficiency and insufficiency has a direct bearing on the study conclusions and makes comparison between studies difficult. However, based on the New Zealand Ministry of Health criteria, many of the absolute values are equal to or above the recommended level of 25-hydroxyvitamin D.

4.1.2.2 Cellular and Molecular Mechanisms

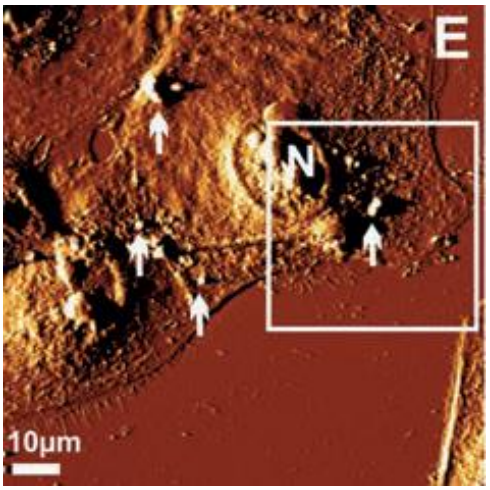
The molecular mechanisms of the genesis of cutaneous lupus, interactions with light and the role of vitamin D are not clear. However, there is evidence that vitamin D may have an immunomodulating effect. Type 1 interferon production by plasmacytoid dendritic cells is important in the pathogenesis of lupus erythematosus and these patients have elevated levels (119). Plasmacytoid dendritic cells are derived from bone marrow and are recognised in the skin by cluster of differentiation (CD) 123 positive staining. Seven skin biopsies of patients with SCLE and 20 biopsies of patients with DLE were examined and plasmacytoid dendritic cells were preferentially located in the dermis compared with the epidermis of these patients (120). A subsequent study of 74 skin biopsies of patients with cutaneous lupus observed that there were two inflammatory populations of plasmacytoid dendritic cells. One population was mainly confined to the perivascular infiltrate and the second was at the dermo-epidermal junction in association with cytotoxic T cells in areas of severe apoptotic keratinocytes (121). Vitamin D exerts many immunomodulating effects including modulating the activity of dendritic cells. When vitamin D is added to dendritic cells stimulated by the plasma of a patient with SLE, the stimulatory effect, as measured by an increase of type 1 interferon gene expression, is largely reversed (122).

4.1.2.3 Ro and Lupus

Ro is a small ribonucleoprotein found mainly in the cell nucleus. The Ro antigen, as determined by the assessment of anti-Ro antibodies in SCLE and SLE, may be important in the pathogenesis of lupus. Homologs of the Ro gene exist in different species. Homologs are related genes from different species, descended from a common ancestral DNA sequence. Homologs of the Ro gene in humans have been identified in the microbe *Deinococcus radiodurans* (123), the worm *Caenorhabditis elegans* (124) and the frog *Xenopus* (125). Genetic homologs usually occur when the gene product continues to be useful for an organism, although its use may be adapted, and Ro may be important in protection against UV damage. *Deinococcus radiodurans* is a eubacterium (characterised by a rigid bacterial wall) and the Ro homolog in this organism has been shown to be important in resisting damage to UV radiation. Organisms which are modified to have Ro homolog inactivated are more sensitive to UV irradiation than the wild type organism (123).

There is evidence about the role of Ro in humans exposed to UV radiation. Experimentally in vitro, human keratinocytes were irradiated with narrow band UV and then imaged by microscopy. Serum from patients with lupus erythematosus was applied to the irradiated cells. The cells were seen to alter their morphology and small bleb like protrusions noted on the keratinocyte surface. The presence of Ro antigen on the surface was limited, mainly, to the small bleb like protrusions, and some submembranous structures also stained with anti-Ro serum (Figure 3).

Figure 3: Bleb like structures staining with anti-Ro antibody (arrow) after narrow band UVB irradiation of human keratinocytes taken from *Reich A et al 2009* (126)



It was therefore postulated that the mechanism of anti-Ro antibody formation is by the extrusion of Ro into the keratinocyte surface by UVB induced damage. This could then trigger an immunological response and the keratinocyte damage seen in lupus (126). It has been noted previously that the position of the plasmacytoid dendritic cell in cutaneous lupus is at the site of epithelial apoptosis (121). Therefore, it is interesting to note in psoriasis, that cathelicidin (LL-37), the expression of which is partly controlled by vitamin D, is important in binding to self-DNA and triggering activation of plasmacytoid dendritic cells to produce interferon (127).

4.1.3 Systemic Lupus and Vitamin D

Skin involvement can be a feature of SLE, but is not a prerequisite for the diagnosis. The 1982 revised criteria for the diagnosis of systemic lupus requires four out of 11 criteria to be present, either serially or simultaneously, during a period of observation. As described previously, the criteria are malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder, haematologic disorder, immunologic disorder and abnormal antinuclear antibody titre (99). Therefore, cutaneous lupus is one part of a clinical spectrum of systemic lupus and of the disease process.

In common with cutaneous lupus, it is standard advice to recommend patients with systemic lupus to practice careful sun protection, thereby increasing their risk of vitamin D deficiency. Patients with SLE have a greater risk of osteoporosis, compared with age-matched controls, and a higher incidence of cardiovascular disease (128). Furthermore, systemic lupus, like cutaneous lupus, is more common in non-Caucasian individuals and more common in females. Reported prevalence of the disease varies around the world but on average in the USA, Spain and the UK is approximately 48.2 per 100,000 (110). This reported prevalence is broadly similar to that reported for cutaneous lupus.

There are many publications examining the role of vitamin D in SLE and a full review is beyond the scope of this thesis. In 2012 Singh and Kamen published a review article of 24 studies of SLE focusing on the association of disease activity and vitamin D status (128). There was one case series, 10 cross-sectional case-control studies, nine cross-sectional cohort studies and four prospective cohort studies. Sixteen of the studies showed an inverse relationship between disease activity and vitamin D levels. The remaining eight

studies failed to show an association, but no study demonstrated that low vitamin D levels were beneficial for patients with SLE.

To date there has not been a randomised, placebo-controlled study to examine the effect of vitamin D supplementation on the activity or biochemical parameters of patients with systemic lupus. Vitamin D has been examined as a risk factor for many autoimmune diseases, and these include diabetes mellitus, multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease (129-133).

4.1.4 Summary

There is a significant weight of evidence showing an association of SLE with low 25-hydroxyvitamin D levels. Only a few studies have examined the association in cutaneous lupus. Laboratory evidence suggests that replacing vitamin D will reverse some of the immunological effects of deficiency, but to date a randomised, placebo-controlled study of the clinical effect of vitamin D supplementation on cutaneous lupus has not been undertaken.

It is theoretically possible that in cutaneous and systemic lupus, the standard advice to protect the skin from sunlight may exacerbate vitamin D deficiency leading to deterioration in the clinical condition. Consideration should be given to routine supplementation.

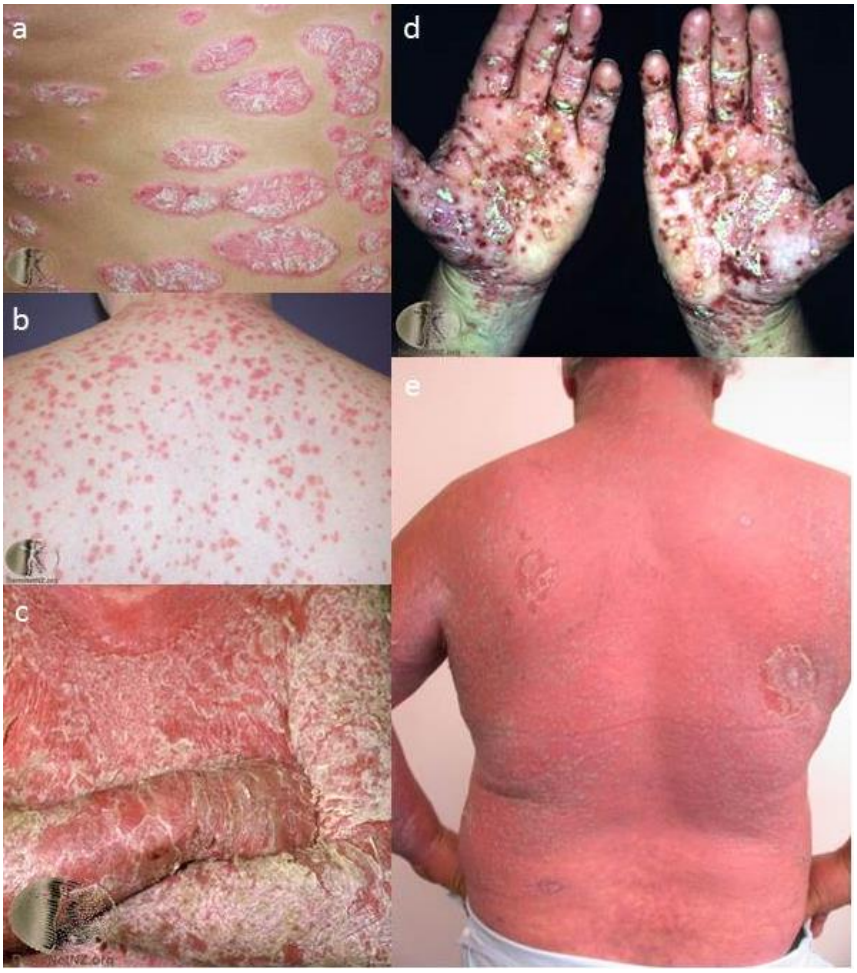
In the New Zealand community Māori and Pacific people, who have darker skin, are more likely to have lower 25-hydroxyvitamin D levels than non-Māori and non-Pacific people. Furthermore, the Māori and Pacific people are more likely to develop SLE. It would be interesting to know if these communities have a higher prevalence of cutaneous lupus than do European New Zealanders, and if patients in New Zealand with cutaneous lupus have lower 25-hydroxyvitamin D levels than healthy controls.

4.2 Psoriasis

Psoriasis is a common inflammatory skin disease affecting between 1 and 2% of the worldwide population (134). It is a disease of uncertain aetiology but is characterised by quick and disordered growth of keratinocytes. The keratinocyte trigger is believed to be due to activation of the cellular immune system, with T cells, dendritic cells and various inflammatory mediators, especially interleukin 17, implicated in the pathogenesis (135, 136). Psoriasis can occur at any time in life but has two peaks at around 20 and then 50 years of age. There is a strong genetic linkage in the aetiology of psoriasis with many identified susceptibility genes, called PSORS (psoriasis susceptibility). It can cause disproportionate psychological disability. External triggering factors are also important, including infection (especially streptococcal), human immunodeficiency virus, many drugs (including lithium, beta blockers, antimalarials, non-steroidal anti-inflammatories and tetracyclines), psychogenic stress and physical trauma (1).

Psoriasis can be located in specific areas only including the scalp, flexures and nails. Clinically, psoriasis presents in different forms including chronic plaque, guttate, erythrodermic, localised and generalised pustular psoriasis (Figure 4).

Figure 4: Types of Psoriasis



a) Chronic plaque b) Guttate c) Erythrodermic d) Localised pustular e) Generalised pustular (a, b, c, d reproduced with permission from DermNet NZ, e personal collection)

There are many different treatment options, depending on the site and severity of disease as well as the patient preference. Topical treatments include steroids, retinoids, anthralin, coal tar and vitamin D_3 analogues. Phototherapy with narrowband UVB light is reserved for more extensive disease. Systemic treatments include methotrexate, cyclosporin, hydroxyurea, fumarates and acitretin. These drugs have specific, and potentially significant, side effect profiles including renal and hepatic impairment (1). More recently, a new class of agent, the biologics, has been developed. These agents exploit the greater knowledge of the immunology of psoriasis and include the tumour necrosis factor α blockers adalimumab, etanercept, infliximab, ustekinumab (interleukin 12 and 23 inhibitors) and secukinumab (interleukin 17 inhibitor) (137, 138). Immunosuppression with infection risk is a particular concern with the biologic agents (137).

As well as being associated with psoriatic arthritis, psoriasis has recently been found to be an independent risk factor for cardiovascular disease including ischaemic heart disease (OR 1.78; 95% CI: 1.51–2.11), cerebrovascular disease (OR 1.70; 95% CI: 1.33–2.17) and peripheral vascular disease (OR 1.86; 95% CI: 1.56–2.21) (139).

4.2.1 Vitamin D and Psoriasis

There has been considerable research around vitamin D and psoriasis in the basic sciences, particularly the sites of distribution of the vitamin D receptor (VDR), which is summarised in Table 6. The VDR is found on many tissues, but was first demonstrated in human skin in 1980 when Feldman et al identified receptors in fresh epidermis, cultured keratinocytes and fibroblasts (140). The VDR was subsequently demonstrated on testing of the uninvolved skin of patients with psoriasis and these were compared with normal controls. The VDR was found in the nucleus of cultured keratinocytes and these were qualitatively and quantitatively similar to the normal controls. This study also incubated keratinocytes of psoriatic patients with 1, 25-dihydroxyvitamin D_3, which inhibited basal cell proliferation in a dose-dependent fashion similar to the response seen from the normal subject. Incubation of the psoriatic keratinocytes also resulted in an induction of terminal differentiation as there were increased numbers of squamous cells and cells with a cornified envelope (141). Several years later, with the development of monoclonal antibodies to the VDR, staining was demonstrated in all layers of the epidermis except the stratum corneum in biopsies of psoriatic plaques. Langerhans cells, macrophages and lymphocytes were also shown to stain for the VDR and non-lesional psoriatic skin specimens showed nearly identical staining patterns (142). The mechanism of increased cornification was further elucidated in 2013 when Hoss et al demonstrated that 1, 25-dihydroxyvitamin D_3 upregulated all five late cornified envelope (LCE) genes (143). A risk factor for psoriasis is a deletion of LCE3B-C genes and this gene cluster encodes proteins in the stratum corneum expressed late in the differentiation of keratinocytes.

There is conflicting evidence around VDR polymorphisms, psoriasis and response to vitamin D supplementation. In 1996 Chen et al examined the VDR messenger ribonucleic acid (mRNA) expression in psoriatic plaques. In patients who showed a > 90% clinical improvement in their psoriasis from applying topical 1, 25-dihydroxyvitamin D_3 (n = 9), there was an increase of 130 ± 37% in VDR mRNA when compared with a placebo control, and in those patients whose lesions did not respond to the topical treatment there was no increase (144). In contrast, Kontula et al in 1997 examined the VDR polymorphisms

in 10 patients who improved, and nine who did not, after the application of calcipotriol cream (a synthetic vitamin D_3 analogue—see Chapter 4, Section 4.2.4) and there was no clear difference between the two groups (145). In a larger study of 90 patients the following year, Mee et al found no difference between VDR genotype and clinical responsiveness to calcipotriol (146). The largest study of genetic polymorphisms of the VDR in psoriasis, published by Park et al in 1999, examined 104 patients compared with 104 healthy controls (147). This study demonstrated a significant increase in the frequency of the A allele in the psoriatic group, compared with the control group, and the tendency for early onset psoriasis (≤40 years old). Odds ratios (95% CI) for psoriasis of AA and Aa genotypes were 5.0 (1.3–19.1) and 2.4 (1.3–4.3) respectively, and odds ratios for early onset of AA and Aa genotypes were 6.4 (1.6–25.0) and 3.1 (1.7–5.9), compared with the control group. A significant association between VDR genotypes and the mean age of onset was observed ($p < 0.05$). The findings suggested that the VDR gene, or others in linkage disequilibrium, could predispose towards psoriasis. However, a later meta-analysis of 11 eligible studies examining the VDR variants (Fok1, Taq1, Apa1 and Bsm1) showed no association with risk for psoriasis (148).Therefore, the evidence is mixed about the genetic ability to respond to vitamin D in psoriasis, although VDR polymorphisms do appear to influence predisposition to psoriasis.

The early phases of psoriasis are characterised by the infiltration of psoriatic skin by plasmacytoid dendritic cells (149). Plasmacytoid dendritic cells can initiate psoriasis by the production of interferon type 1 (α) (150). Furthermore, proteins of the VDR pathway are expressed on plasmacytoid dendritic cells and vitamin D impairs the capacity of human plasmacytoid dendritic cells to induce T-cell proliferation and secretion of interferon-α (151). These studies add further weight for the use of vitamin D as a therapy for psoriasis.

Three studies have examined 25-hydroxyvitamin D status in psoriasis. Orgaz-Molina et al published a case-control study in 2012 from Spain (152). Forty-three patients with psoriasis were compared with 43 age- and sex-matched controls over a four-week period. Mean serum 25-hydroxyvitamin D levels were significantly lower in the psoriatic patients (60.9 ± 19.5 nmol/l) compared with the control group (73.7 ± 23.4 nmol/l). A multivariate logistic regression showed a strong association between psoriasis and 25-hydroxyvitamin D less than 75 nmol/l (OR 2.89; 95 % CI: 1.02–7.64, $P < 0.03$) after adjustment for BMI, age, sex, dietary vitamin D intake, total sun exposure and skin type as confounding factors.

In Italy, Gisondi et al under took a case-control study of 145 patients with psoriasis, 112 patients with rheumatoid arthritis and 141 healthy controls (153). 25-hydroxyvitamin D deficiency, defined as 25-hydroxyvitamin D level < 50.0 nmol/l, was 57.8% in patients with psoriasis, compared with 37.5% of those with rheumatoid arthritis and 29.7% of healthy controls ($p < 0.001$). In logistic regression analysis, vitamin D deficiency was associated with psoriasis independently of age, sex, BMI, calcium, PTH levels and season of sampling (OR 2.50; 95% CI: 1.18–4.89, $p < 0.01$).

Wilson studied 25-hydroxyvitamin D in 148 patients with psoriasis compared with 5,693 patients without psoriasis from the 2003–2006 National Health and Nutrition Survey. The major limitation was that psoriasis was self-reported although 148 out of a total of 5,841 represents 2.5% of the population, so most participants would seem to have been identified based on the accepted overall prevalence of 1–2% in the general population. There was no significant difference in 25-hydroxyvitamin D levels between the two groups, with mean 25-hydroxyvitamin D levels in patients with psoriasis being 60.4 nmol/l (95% CI: 56.9–

64.1 nmol/l) compared with 58.9 nmol/l (95% CI: 56.9–61.2 nmol/l) in those who did not report psoriasis (p = 0.37) (154).

In 2014 Merola et al investigated the association between dietary, supplementary and total vitamin D intake and incident psoriasis in women, and concluded that there was no change in the association between vitamin D intake and incident psoriasis, after adjusting for hypertension, cardiovascular disease, diabetes and hyperlipidaemia (155). This study identified only 502 cases of psoriasis from a population of 70,437 female nurses enrolled in the Nurse's Health study. The proportion of nurses identified (0.7%) suggests that not all nurses with psoriasis were identified in a disease that has a 1–2% prevalence rate and perhaps under reporting may have affected the results.

Table 6: Vitamin D and psoriasis (basic science)

Author	Key finding	Significance
Feldman 1980 (140)	VDR demonstrated in human keratinocytes and fibroblasts	First description of VDR in human skin
Smith 1988 (141)	Psoriatic keratinocytes have 1,25 dihydroxyvitamin D_3 receptors 1,25 dihydroxyvitamin D_3 causes dose-dependent inhibition of proliferation and induction of terminal differentiation	VDR present in psoriatic plaques
Park 1991 (147)	VDR polymorphisms associated with psoriasis	Allelic variation could predispose to psoriasis
Milde 1991 (142)	Expression of VDR in all layers of epithelium except stratum corneum	
Chen 1996 (144)	Induction of VDR mRNA expression in psoriatic plaques correlates to clinical response to 1,25 dihydroxyvitamin D_3	Antiproliferative effect of 1, 25 Vit D closely associated with expression of its receptor
Kontula 1997 (145)	No clear cut difference between calcipotriol responders and non-responders when VDR polymorphisms examined	VDR polymorphism not significantly associated with psoriasis
Mee 1997 (146)	No correlation between VDR genotype and clinical responsiveness to calcipotriol	VDR polymorphism not significantly associated with psoriasis
Wollenberg 2002 (149)	Plasmacytoid dendritic cells identified in psoriatic plaques	Uncertain
Nestle 2005 (150)	Plasmacytoid dendritic cells activated in psoriatic plaques to produce interferon-α	Novel innate immune pathway for triggering psoriasis opening new therapeutic options
Hoss 2013 (143)	1,25 dihydroxyvitamin D upregulates late cornified envelope (LCE) 3A-E genes	Amelioration of absent LCE 3 B-C gene function in psoriasis
Karthaus 2014 (151)	Vitamin D controls human plasmacytoid dendritic cell function	Vitamin D as a therapeutic option

VDR = Vitamin D receptor.

The presence of the VDR within the epidermis of both normal and psoriatic skin suggests a function for vitamin D within the epidermis but the role is not clear from these studies. However, this area is explored further in Section 4.2.1.1. The observational clinical studies in psoriasis are conflicting and difficult to compare. For example, the severity of psoriasis between the studies is not comparable as different scoring systems are used or not reported. Both of the studies with large control groups suggest there is no association between low vitamin D levels and psoriasis.

4.2.1.1 Vitamin D, Psoriasis and Interleukin 17

Interleukin-17 (IL-17) has emerged as a key cytokine in the pathogenesis of psoriasis (136). Keratinocytes respond strongly to IL-17, produced by T-cell subsets including CD4+, CD8+, αβ and $_{Y}$δ T cells. The IL-17 producing cells are all encompassed by the term Th17 cells. IL-17 synergises with other cytokines, for example tumour necrosis factor–α, to induce key gene products.

Vitamin D deficient CD4+ cells over produce IL-17 in vitro and 1, 25 dihydroxyvitamin D_3 inhibits the development of Th17 cells in CD4+ cell cultures (156). The mechanism of 1, 25 dihydroxyvitamin D_3 repression of IL-17 is due to transcriptional repression mediated by the VDR (157) .

Twenty-five 25-hydroxyvitamin D deficient individuals were compared with a control group of healthy individuals (158). The 25-hydroxyvitamin D deficient group was treated with monthly increasing doses of cholecalciferol of 2,000, 4,000 and 8,000 IU per day and as the 25-hydroxyvitamin D levels increased, IL-17 producing T cells were reduced up to 40% in the cholecalciferol supplemented group.

Forty-eight patients with psoriasis were compared with 40 age-, sex-, skin type- and socioeconomic-matched controls. Mean IL-17 was significantly higher (10.54 ± 0.38 pg/ml) in patients than in controls (3.72 ± 0.26 pg/ml) and 25-hydroxyvitamin D was lower (52.5 ± 9.1 nmol/l) in patients than in controls (92.4 ± 12.6 nmol/l) ($p < 0.001$) (159).

CD4+ and CD8+ IL-17 T cells have been demonstrated in psoriatic plaques (160). Eighteen patients with psoriasis had one plaque of psoriasis treated with calcipotriol ointment (50µg/g) (see Chapter 4, Section 4.2.4) and the other with an ointment vehicle twice a day for 14 days. Skin biopsies were collected after the treatment and a significant decrease in CD8+ IL-17 T cells was demonstrated concomitant with the clinical improvement (161). Antimicrobial peptides are discussed in Chapter 4, Section 4.4. However, the treatment of psoriatic plaques by calcipotriol suppresses the production of psoriasin and koebnerisin, which are antimicrobial peptides differentially induced in psoriatic skin. These antimicrobial peptides act as chemoattractants and amplify inflammation in psoriasis and they are regulated by Th17 cytokines including IL-17 (162).

These studies suggest there may be a role at a cellular level, in psoriasis, for an interaction between vitamin D and IL-17.

4.2.2 Phototherapy, Vitamin D and Psoriasis

Phototherapy is an established treatment for psoriasis and narrowband UVB is commonly used (1). Patients with psoriasis are placed within a large cabinet and irradiated with light from narrowband UVB bulbs. The Phillips TL01 narrowband bulbs emit UVB in a narrowband between 311 and 313 nm which falls within the action spectrum for psoriasis which is 304 and 313 nm (163). The effect of phototherapy on vitamin D levels has been studied.

An early small study of 16 patients examined the effect of broadband UVB (290–320 nm) combined with the addition of oral 1, 25-dihydroxyvitamin D_3 (calcitriol) (164). Patients were randomly assigned to receive either placebo or 1, 25-dihydroxyvitamin D_3 in doses of 0.5 to 2 µg daily for three weeks, and then they

received a course of approximately 21 treatments of broadband UVB over five weeks. Both groups experienced an elevation in 25-hydroxyvitamin D by the end of the study period. A significant difference ($p < 0.05$) in 1, 25-dihydroxyvitamin D_3 was detected between final levels in the actively treated group (156.3 ± 64.7 pmol/l) and the placebo group (91.5 ± 51.2 pmol/l) at the end of the study. The clinical effect was reported separately and there was no significant difference between the Psoriasis Area and Severity Index (PASI) scores in the two groups (165). The finding that broadband UVB increased 25-hydroxyvitamin D_3 levels in psoriasis was confirmed by a later study of 24 post-menopausal Caucasian women (166).

Narrowband UVB (310–315 nm) has also been demonstrated to increase 25-dihydroxyvitamin D levels in patients with psoriasis as well as atopic dermatitis and vitiligo (167). In patients with an initial level of 25-hydroxyvitamin D (<80 nmol/l), a significant ($p < 0.001$) 30–60% increase was observed depending on the UVB dose used. Comparing narrowband UVB to broadband UVB in a study of 68 Caucasian patients with psoriasis, both types of treatment increased the 25-hydroxyvitamin D_3 level (broadband UVB 94.6 ± 42.4 nmol/l to 173.2 ± 49.2 nmol/l and narrowband UVB 86.9 ± 29.7 nmol/l to 138.0 ± 43.9 nmol/l), but the increase was significantly less for narrowband UVB ($p = 0.008$) (168). The finding that narrowband UVB increases 25-hydroxyvitamin D has been found in multiple other settings, including psoriatic patients in the Irish winter, healthy women in the Finnish winter, Polish psoriatic patients, Finnish haemodialysis patients and Swiss patients with vitiligo, mycosis fungoides and Mallorca acne (169-173). Narrowband UVB has also been shown to be more effective at increasing 25-hydroxyvitamin D than low dose oral cholecalciferol (174). Healthy adults with a 25-hydroxyvitamin D level < 75 nmol/l were treated with either 20 µg of oral cholecalciferol daily for four weeks or 12 exposures to narrowband UVB. The group receiving narrowband UVB had a significantly larger increase in 25-hydroxyvitamin D (41.0 nmol/l, 95% CI: 34.8–47.2) than did the oral cholecalciferol group (20.2 nmol/l, 95% CI: 14.6–26.0) at four weeks ($p < 0.001$). Twelve patients with psoriasis were compared with 15 healthy subjects, who were all given a course of narrowband UVB and supplemented with cholecalciferol 20µg daily. Cholecalciferol was started on average 3.3 months prior to UVB in the psoriatic patients and on average 3.4 months prior to UVB in the controls. 25-hydroxyvitamin D levels increased in both the patients (13.2 nmol/l 95% CI: 7.2–24.9, $p = 0.0029$) and controls (17.0 nmol/l 95% CI: 6.7–21.0, $p < 0.001$) after nine UVB exposures. PASI scores improved from 8.7 (range 4.0–16.2) at baseline to 6.4 (range 2.1–12.8) at the ninth exposure (175). However, as previously discussed, because of the biology of vitamin D synthesis in the skin, there is an upper threshold beyond which light is unable to increase the 25-hydroxyvitamin D_3 level (64).

In a modern day version of heliotherapy (see Chapter 2, Section 2.2.3), 20 patients who attended the Norwegian Health Centre in Gran Canaria were studied (176). These patients received sun therapy for 15 days and a 72.8 % (SD 18) reduction in the PASI was seen, accompanied by an increase in 25-hydroxyvitamin D from 57.2 ± 14.9 nmol/l to 104.5 ± 15.8 nmol/l ($p < 0.0001$), and 1, 25-hydroxyvitamin D_3 levels rose from 146.5 ± 42.0 to 182.7 ± 59.1 pmol/l ($p = 0.01$). Interestingly, this was also accompanied by a significant reduction in low-density lipoprotein to high-density lipoprotein ratio and a reduction in haemoglobin A_1c levels.

Phototherapy has been demonstrated to elevate 25-hydroxyvitamin D levels in healthy participants and patients with psoriasis. The elevation in 25-hydroxyvitamin D levels is associated with clinical improvement in psoriasis as measured by the PASI score. However, association does not prove causation.

4.2.3 Clinical Studies of Oral Vitamin D in Psoriasis

There are reports of the use of oral vitamin D in the treatment of psoriasis. In this section they are discussed by study types; case report, uncontrolled open label, prospective, randomised open and uncontrolled open label. They are summarised in Table 7.

In 1985 Morimoto et al described an 81-year-old man with osteoporosis and psoriasis. The patient's psoriasis had been treated for over 30 years without benefit. The patient was treated with 1α-hydroxyvitamin D_3 0.75 µg/day and within three months the psoriasis had almost completely resolved (177). Morimoto et al then went on to describe two patients who were treated with 1α 25-dihydroxyvitamin D_3 0.5 µg/day for six months who experienced a "moderate improvement" (178).

In 2012 in a case report, Werner de Castro et al describe a 52-year-old woman who was given adalimumab 40 units once every two weeks for rheumatoid arthritis who developed a psoriasiform flare. Adalimumab is a tumour necrosis factor α (TNF-α) inhibitor that is used to treat inflammatory disorders including rheumatoid arthritis and severe psoriasis. Paradoxically, it can exacerbate psoriasis in some patients. She was also taking methotrexate 10 mg weekly and prednisone 20 mg once daily. She was found to have a 25-hydroxyvitamin D level of 18.5 nmol/l. This level would be categorised as mild to moderate deficiency in the current New Zealand Ministry of Health definitions. The psoriasiform lesions resolved when the deficiency was treated with vitamin D_3 50,000 UI/week for eight weeks, along with calcium carbonate 1,000 mg daily and sodium alendronate 70 mg weekly. Her 25-hydroxyvitamin D level rose to 71.4 nmol/l and her adalimumab was continued (179).

During the 1980s there was a series of larger studies published using oral vitamin D in the management of psoriasis. In the reports from Osaka University Medical School, Japan, it is not clear that different studies are being referred to, as the content of the reports is similar, suggesting multiple papers in different journals derived from the same patient group. The separate published studies from this group are reported individually rather than amalgamated for this review.

The first study (open label, uncontrolled) reported the results of the use of 1α-hydroxyvitamin D_3 in seven patients with psoriasis. There were six males and one female with an average age of 54 years. The pre-treatment state was recorded for six months and then observation of the effect of oral 1α-hydroxyvitamin D_3 1.0 µg daily for six months was recorded. Previously, all patients were resistant to treatment with topical steroids. Some had also received phototherapy and systemic steroids. It was concluded that four of seven patients had either complete remission (defined as complete flattening of plaques, including borders, and percentage of area improved as 95% or more) or marked improvement (defined as nearly complete flattening of all the plaques still palpable and area improved 50–90%). No adverse reactions were noted. The serum calcium increased significantly but remained within the normal range and there was no significant change in serum phosphorus, PTH, calcitonin, 25-hydroxyvitamin D_3 (baseline mean 27.4 ± 4.0 nmol/l) and 1, 25-dihydroxyvitamin D_3. The results were encouraging; however, there was no attempt to power the study adequately, it is not clear if the same observer did all the grading of the psoriasis severity and the grading system was unorthodox. The lack of a control group significantly weakened the study (180).

A larger open label study from the same group examined the effect of 1α-hydroxyvitamin D_3 in 17 patients with psoriasis. There were 14 males and three females with an average age of 47 years. Using a similar protocol to the previous study, the patients were given 1.0 µg/day for six months. The grading system was different and complete remission was defined as "+4", marked improvement as "+3" and moderate improvement "+2". More than moderate improvement was observed in 13 of the 17 patients after 2.7 months of treatment. Three patients had a slight aggravation "−1" at four, five and six months. No adverse effects were noted and no change in the biochemical parameters were seen, when compared with 24 age-matched controls (181).

In the same year as the two previously described studies, the Japanese group described a significantly larger study with a group of 40 patients. This study examined the effect of 1.0 µg/ day of 1α-hydroxyvitamin D_3 in 17 patients for six months, 0.5 µg/day 1α, 25-dihydroxyvitamin D_3 in four patients for six months and the use of topical 1α, 25-dihydroxyvitamin D_3 at a concentration of 0.5 µg/g of base for eight weeks in 19 patients. The 17 patients have the same results as the 17 described in the previous paragraph and presumably was the same group reported twice in different journals. In the group given 0.5 µg/day oral 1, 25-dihydroxyvitamin D_3, one patient had an improvement of "+2" and in the topically treated group, 16 of 19 patients had a "+2" improvement. In the group of four, no adverse effects were reported but there was a significant rise in serum calcium levels although not in the other parameters (182). Morimoto et al republished their results from the group of 40 patients in 1989 (183). This report contains a more detailed assessment of the severity of the psoriasis not recorded in the previous publications, named the "Area Severity Index" (ASI), a modified version of the now widely used Psoriasis Area Severity Index (PASI). The severity of the psoriasis, as measured by the ASI, was correlated with the serum 1, 25-dihydroxyvitamin D_3 level by Spearman's rank correlation analysis, showing a significant negative correlation ($p < 0.05$, $r = -0.353$). The method of ascertaining the ASI score three years after publication of the original group is not discussed and the integrity of the ASI calculation may be in some doubt.

Smith et al published a study in 1988 examining the effect of 1, 25-dihydroxyvitamin D_3 on 14 patients with psoriasis and the double-blinded application of topical 1, 25-dihydroxyvitamin D_3 in three patients (141). This study examined the clinical effect as well as the effect at a cellular level on cultured keratinocytes and fibroblasts. Fourteen patients were given 1, 25-dihydroxyvitamin D_3 initially 0.25 µg once or twice daily, and if they remained normocalcaemic, the dose was increased to a maximum of 2.0 µg/day, with five patients achieving that dose. All psoriasis treatments were discontinued for two weeks prior to starting, and the duration of the treatment is not explicitly stated, but at the time of publication six patients had been on treatment for 12 months. The clinical grading of the psoriasis severity was on a 5 point scale, with "0" being no change and "+4" being > 75% improved. Keratinocytes were successfully cultured from two patients with psoriasis, and they were shown to have receptors for 1, 25-dihydroxyvitamin D_3 that were quantitatively and qualitatively similar to those in normal keratinocytes. Basal cell proliferation was inhibited in a dose-dependent fashion by 1, 25-dihydroxyvitamin D_3 in a similar manner to that of keratinocytes derived from a patient without psoriasis. Further incubation of psoriatic keratinocytes with 1, 25-dihydroxyvitamin D_3 resulted in an induction of terminal differentiation. Ten of the 14 patients showed a moderate improvement, with seven being a "+4" and none showing no change. Three patients had complete clearing that was sustained with maintenance treatment. Four patients were withdrawn, two because of hypercalcuria and

two for personal reasons. These four patients had 0, no change; +1, minimal improvement up to 25% improved; or +2, 26% to 50% improved, poorer responses than the other 10 participants. The clinical response of the plaques was typically finer with less adherent scale in the first month of treatment, with gradual thinning of the plaques with central clearing and then peripheral extension. In the topically treated group, two patients improved with a +3 grade and one with a +4 grade. The in vitro work in this study demonstrated that keratinocytes from patients with psoriasis would respond to orally administered 1, 25-dihydroxyvitamin D_3 and that it was safe and effective in some patients. However, the measure of psoriasis severity was not standardised and there was no control in the oral group.

Holland et al gave 15 patients oral 1-hydroxyvitamin D_3 1 µg/ day and then examined keratin expression by monthly sampling of psoriatic plaques for —four to six months. The total duration of therapy was not stated but therapy was administered for about six months. Clinical resolution occurred in seven patients, three showed an incomplete response and five showed no response. The changing keratin expression supported the view that 1-hydroxyvitamin D_3 inhibited keratinocyte proliferation and promoted differentiation (184).

In 1993 in the French literature, Boisseau-Garsaud et al reported five patients (aged 6, 16, 36, 58 and 79 years) who were successfully treated with oral 1, 25-dihydroxyvitamin D3 (calcitriol); however, the exact duration of treatments was not accurately recorded but seems to range from one month to seven years (paper translated by Professor R Ramsay, Emeritus Professor of French, The University of Auckland, 2014). Four had erythrodermic and/or pustular psoriasis and two had concomitant hypocalcaemia. The fifth patient had pseudohypoparathyroidism. The patients were treated with calcitriol, a synthetic vitamin D analogue. Of the five patients, four showed improvement within two to four weeks, although the fifth patient with pseudohypoparathyroidism was reported has having “no psoriasis” lesions present after seven years of treatment. Objective measures of psoriasis, such as the PASI, were not recorded so the assessment is subjective (185).

In 1996 Perez et al published a single centre open label study on the effect of 1, 25-dihydroxyvitamin D_3 in 85 patients, particularly examining the long term safety and efficacy (186). Patients had to have 15% of the body surface area involved with chronic stable plaque psoriasis or erythrodermic psoriasis. Before enrolment, all patients stopped systemic therapy or phototherapy for at least 30 days, and topical medications, other than emollients, for at least 14 days. They were started on 0.5 µg of 1, 25-dihydroxyvitamin D_3 which was increased in increments of 0.5 µg every two weeks provided the serum and 24-hour urinary calcium remained in the normal range. Eighty-five patients were recruited (62 men and 23 women with a mean age of 46 years). The mean (SD) baseline PASI score was 18.4 (± 1.0) and at six months and 36 months the score was reduced to 9.7 (± 0.8) and 7.0 (± 1.3), respectively ($p < 0.001$). The overall clinical assessment showed that 88.0% of all patients on oral 1, 25-dihydroxyvitamin D_3 had some improvement in their disease and, of these, 26.5% had complete clearance, 36.2% had moderate improvement, 25.3% had slight improvement and 12% had no change in their disease activity. Serum calcium concentrations and 24-hour urinary calcium excretion increased by 3.9% and 148.2% but not outside the normal range. Creatinine clearance decreased by 13.4% from baseline in the first six months but then remained unchanged after three years follow-up. There was no significant difference in the bone density in a two-year analysis. This study showed that 1, 25-dihydroxyvitamin D_3 could be an effective and safe treatment for psoriasis. It does not state how many patients had chronic plaque psoriasis, as opposed

to erythrodermic psoriasis, nor if only one observer measured the PASI score given the inter-observer variability, but it was the first to use a standardised assessment. As with the other studies, lack of blinding and a control group introduces the potential for considerable bias.

Acitretin (a systemic retinoid) and oral calcitriol were combined for the treatment of plaque psoriasis in an open study published by Ezquerra et al in 2007 (187). The same investigator measured the PASI score and patients were randomised into two groups with each group receiving acitretin initially 25 mg per day for 45 days and then 25 mg on alternate days for 45 days. The other group, in addition, received 0.25 µg 1, 25-dihydroxyvitamin D_3 daily. A total of 40 patients were enrolled, 21 females and 19 males with a mean age of 61 years. The results suggested that a faster reduction in PASI could be achieved by combining the treatments rather than using acitretin alone. The method of randomisation and the clinical meaningfulness of the PASI change were not discussed. There was no statistical analysis published between the PASI end points in the two groups.

In an open label study from Brazil, nine patients with psoriasis were supplemented with 35,000 IU vitamin D daily for six months. The precise form of vitamin D is not stated but is presumed to be cholecalciferol. Interestingly in this group of nine patients, the mean (SD) 25-hydroxyvitamin D_3 levels were 37.2 (± 18.5) nmol/l which is in the below recommended level but not deficient range for the New Zealand Ministry of Health. The clinical condition of all the patients improved. The absolute PASI scores were not reported but the difference before and after was significant statistically with $p < 0.01$. PASI correlated negatively with 25-hydroxyvitamin D_3 levels ($r = -0.56$, $p = 0.001$). The 25-hydroxyvitamin D_3 levels in the patients increased from a baseline of 37.2 (± 18.5) to 265.3 (± 79.6) nmol/l ($p < 0.0001$) without laboratory or clinical signs of toxicity (188).

Table 7: Summary of clinical studies of oral vitamin D supplementation in psoriasis

Author/date	Type of study	Vitamin D type used	Number of patients	Demographic details (age, sex, setting)	Results
Morimoto 1985 (177)	Case report	1α-hydroxyvitamin D_3	1	81 yrs. Male. Hospital.	Complete resolution
Morimoto 1987 (178)	Case report	1α, 25-dihydroxyvitamin D_3	2	14 & 5 yrs. Males. Hospital.	Moderate improvement
Werner de Castro 2012 (179)	Case report	Cholecalciferol	1	52 yrs. Female. Hospital.	Resolution of adalimumab induced psoriasis
Takamoto 1986 (180)	Uncontrolled open label	1α-hydroxyvitamin D_3	7	Mean 53.6 yrs. 6 male, 1 female. Hospital.	4 of 7 complete resolution 2 minimal improvement
Morimoto 1986 (182)	Uncontrolled open label	Group 1:1α-hydroxyvitamin D_3 Group 2: 1α, 25-dihydroxyvitamin D_3	40	Group 1: • Mean 47 yrs. • 14 male, 3 female. Group 2: • Mean 38 yrs. • 4 male. Hospital.	Group 1: Improvement in 13 patients • (n = 17 oral 1.0 µg/day 1α-hydroxyvitamin D_3 for 6 months) Group 2: Improvement in 1 patient • (n = 4 oral 0.5 µg/day 1α, 25-dihydroxyvitamin D3 for 6 months)
Morimoto 1986 (181)	Uncontrolled open label	1α-hydroxyvitamin D_3	17	Mean 47 yrs. 14 male, 3 female. Not stated.	More than moderate improvement in 13 patients
Smith 1988 (141)	Uncontrolled open label	1, 25-dihydroxyvitamin D_3	14	Mean 41.7 yrs. Male 9, female 5. Hospital.	10 of 14 significant clearing 3 complete clearing
Morimoto 1989 (183)	Uncontrolled open label	1α-hydroxyvitamin D_3 1, 25-dihydroxyvitamin D_3	40 (21 in oral group, 19 in topical group)	Mean age 44 yrs. Gender not stated. Hospital.	Moderate/remarkable improvement/complete remission 13 of 17 patients • (n = 17 oral 1.0 µg/day 1α-hydroxyvitamin D_3 for 6 months) Moderate/remarkable improvement/complete remission 1 of 4 patients • (n = 4 oral 0.5 µg/day 1α, 25-dihydroxyvitamin D_3 for 6 months)
Holland 1989 (184)	Uncontrolled open label	1α-hydroxyvitamin D_3	15	Age not stated. Male 6, female 9. Hospital.	Resolution 7 patients Incomplete resolution 3 patients Lack of response 5 patients
Boisseau-Garsaud 1993 (185)	Uncontrolled open label	1, 25-dihydroxyvitamin D_3 (calcitriol)	5	Mean 39 yrs. Gender not stated. Hospital.	Successful, 4 of 5 patients improving in 2–4 weeks.
Perez 1996 (186)	Uncontrolled open label	1, 25-dihydroxyvitamin D_3 (calcitriol)	85	Mean 4 yrs. 6 Male 62, female 23. Hospital.	88.0% some improvement (26.5% complete, 36.2% moderate, 25.3% slight improvement)
Ezquerra GM 2007 (187)	Prospective randomised open	1,25-dihydroxyvitamin D_3 (calcitriol) 0.25 µg/day and acitretin 0.25–0.4 mg/kg/day	40	Mean not stated. Median 61 yrs. Males 19, Females 21. Hospital.	Faster reduction in PASI with combination (p = 0.05) but no significant difference in PASI between the two groups at day 45.
Finamor DC (188)	Uncontrolled open label	Vitamin D 35,000 IU per day for 6 months	9	Mean 45.3 yrs Males 4 Female 5 Hospital	PASI scores not given but p = 0.0023 Negative correlation between PASI and 25-hydroxyvitamin D (r = −0.56, p = 0.001)

Yrs = Years.

4.2.3.1 Quality of Included Studies of Oral Vitamin D in Psoriasis

The level of the quality of evidence of the use of oral vitamin D in the management of psoriasis is summarised in Table 13. The level of quality-underlying methodology rating is based on the GRADE approach (see Appendix 2) and Jadad score (189). Overall, the quality of evidence is low.

Table 8: Summary of quality of evidence of the use of oral vitamin D in psoriasis

Author/date	Level of quality Underlying methodology	Jadad score	Random allocation	Concealed allocation	Blinding	Intention to treat	Risk of bias
Morimoto 1985	Very low	N/A	N/A	N/A	N/A	N/A	High
Morimoto 1987	Very low	N/A	N/A	N/A	N/A	N/A	High
Werner de Castro 2012	Very low	N/A	N/A	N/A	N/A	N/A	High
Takamoto 1986	Very low	0	No	No	Not reported	N/A	High
Morimoto 1986	Low	0	No	No	Not reported	N/A	High
Morimoto 1986	Low	0	No	No	Not reported	N/A	High
Smith 1988	Very low	0	No	No	Not reported	N/A	High
Morimoto 1989	Low	0	No	No	Not reported	N/A	High
Holland 1989	Low	0	No	No	Not reported	N/A	High
Boisseau-Garsaud 1993	Very low	0	No	No	Not reported	N/A	High
Perez 1996	Moderate	0	No	No	Not reported	N/A	High
Ezqerra 2007	Moderate	1	Yes	Not reported	Not reported	Not reported	Medium
Finamor 2013	Very low	0	No	N/A	N/A	N/A	High

N/A = Not applicable.

4.2.4 Clinical Studies of Topical Vitamin D in Psoriasis

Following the discoveries that vitamin D could alter keratinocyte activity in psoriasis, topical agents were developed. The hypercalcaemic effects of systemic vitamin D derivatives limited its use. A vitamin D_3 analogue was tested called MC 903, and it was subsequently named calcipotriol. In animal studies, calcipotriol was found to be a potent inducer of cell differentiation, to inhibit cell proliferation and DNA synthesis in concentrations comparable to 1, 25-dihydroxyvitamin D_3, and was at least 100 times less active in causing hypercalciuria, hypercalcaemia and bone calcium mobilisation if given orally or intraperitoneally, compared with 1, 25-dihydroxyvitamin D_3 and 1α-hydroxyvitamin D_3 (190).

In an early human clinical study, calcipotriol was found to have a significantly beneficial effect in psoriasis (191). A double-blind, dose-ranging study of 30 patients, using a modified PASI scoring system, showed a significant improvement in erythema, thickness and scaling of psoriatic plaques, and this was reflected histologically. There was no change in serum calcium levels. Subsequent double-blinded, left-right within-patient comparisons went on to demonstrate the effectiveness and safety of topical calcipotriol in the treatment of psoriasis (192-194).

4.2.5 Summary

In the 1980s and early 1990s, when it was recognised that topical vitamin D analogue treatments could be a safe and effective treatment for psoriasis, the focus of research moved away from the use of oral vitamin D. The quality of published evidence for the use of oral vitamin D supplements in the management of

psoriasis is low. Therefore, the role of oral vitamin D_3 as a treatment for psoriasis is uncertain. The VDR is present in the skin and evidence at a cellular level supports a modifying role for vitamin D in psoriasis. To examine if vitamin D_3, potentially a relatively safe intervention for a common disorder, has a meaningful clinical effect in psoriasis, a double-blind, placebo-controlled study has been undertaken and is presented in Chapter 6 of this thesis.

4.3 Other Skin Diseases and Vitamin D

The role of vitamin D in other skin disorders has been extensively investigated and a thesis on skin disease and vitamin D would not be comprehensive without concise discussion of the wider field. This section discusses the literature around other skin diseases and vitamin D. The section includes atopic dermatitis, skin cancer and sun-seeking behaviour, vitiligo, systemic sclerosis, Behçet's disease and miscellaneous skin disease.

4.3.1 Atopic Dermatitis

Atopic dermatitis (or eczema) is a common inflammatory skin disease usually arising in early childhood. It typically starts in infancy on the face, then in childhood commonly localises to the flexures. It has a complex aetiology, both genetic and environmental (1). The recent identification of loss of function filaggrin mutations in some patients with atopic dermatitis has been a significant advance in the understanding of the disease (195). Filaggrin mutations are not the only significant factor, as patients without the common filaggrin mutations who have atopic dermatitis may have alterations in ceramides (196).

A few studies have examined the effect of maternal intake of vitamin D and the subsequent risk of the development of atopic dermatitis in children and found contradictory results. A 2007 prospective pre-birth cohort study, designed to examine recurrent wheeze in children, also looked at eczema and found that maternal dietary intake of vitamin D was not associated with risk of early childhood eczema ($n = 428$, $p = 0.58$) (197). However, a publication the following year showed that children whose mothers had a 25-hydroxyvitamin D level in pregnancy of > 75 nmol/l had an increased risk of eczema on examination at nine months (OR 3.26; 95% CI: 1.15–9.29) (198). Finally, a 2011 prospective cohort study found that children whose mothers consumed > 4.31 µg/day of vitamin D had a significantly reduced risk of eczema (adjusted OR 0.64; 95%CI: 0.43–0.97) (199).

In Australia, the prevalence of dermatitis is related to latitude, with children living in southern latitudes more likely to have eczema than those living in the north (200). Furthermore, a two-week course of heliotherapy in the Canary Islands, latitude 28.6° N, has been demonstrated to improve 25-hydroxyvitamin D levels and atopic dermatitis (201).

There are three cross-sectional studies of atopic dermatitis patients examining the association between severity of disease and 25-hydroxyvitamin D levels, and these are summarised in Table 9.

Table 9: Cross-sectional studies examining the severity of atopic dermatitis and vitamin D

Author/date	Age (years)/sex	Study population	Control group	Conclusion
Peroni 2011 (202)	Mean age 5.6 Male (n = 20) Female (n = 17)	Hospital	No	Lower, compared to higher 25-hydroxyvitamin D levels, related to increased severity of atopic dermatitis (p = 0.05) Negative correlation between SCORAD and 25-hydroxyvitamin D levels r = −0.49, p = 0.002
Chui 2013 (203)	Median age 3 Male (n = 40) Female (n = 54)	Hospital	No	No significant correlation between 25-hydroxyvitamin D levels and SCORAD (r = −0.001, p = 0.99)
Samochocki 2013 (204)	Mean age 29.9 Male (n = 44) Female (n = 51)	Not reported	Yes	No significant correlation between SCORAD and 25-hydroxyvitamin D_3 levels (p value not given)

SCORAD = SCOring Atopic Dermatitis; a measure of the severity of atopic dermatitis.

The results are inconsistent with no clear trend. However, Samochocki supplemented 20 of 95 patients who had very low 25-hydroxyvitamin D_3 levels (between 10 and 37 nmol/l) in an unblinded fashion and observed a significant improvement in SCORAD from mean (SD) 37.1 (± 15.2) to 20.8 (± 9.4) ($p < 0.001$).

There are three reported randomised control intervention studies supplementing vitamin D in patients with atopic dermatitis and these are summarised in Table 10.

Table 10: Interventional studies in atopic dermatitis with vitamin D

Author/date	Type of study	Age (years)/sex	Study population	Vitamin D type, dose, duration	Conclusion
Sidbury 2008 (205)	Randomised double-blind placebo controlled	Median 7 Male (n = 6) female (n = 5) (5 active, 6 placebo)	Hospital and community	Ergocalciferol 1,000 u once daily for 1 month	No significant difference in EASI score
Javanbakht 2011(206)	Randomised double-blind placebo controlled	Overall mean age not reported Male (n = 10) Female (n = 36) (45 completed, 11 placebo, 12 active vitamin D, 11 vitamin E, 11 vitamin D & E)	Hospital and private clinics	Cholecalciferol. 1,600 IU once daily for 60 days	No significant difference in SCORAD between control and vitamin D group
Amestejani 2012 (207)	Randomised double-blind placebo controlled	Mean 23.3 Gender not reported (30 active, 30 placebo)	Hospital	Cholecalciferol. 1,600 IU once daily for 60 days	Significant difference in treatment group ($p < 0.05$) using SCORAD and TIS

EASI = Eczema Area and Severity Score, SCORAD = Scoring Atopic Dermatitis, TIS = Three Item Severity Score.

None of these studies had a prior estimate of sample size needed to detect a significant difference, and were small in size, with the Sidbury study having just 11 patients. Javanbakht divided the sample into four groups of between 10 and 11 patients. The patients were adults rather than children, with an average age of the four groups between 21.2 and 29.0 years of age. This study examined placebo, vitamin D alone, vitamin E alone and a combination of vitamin D and E. Therefore, the individual comparison groups may not have been powered sufficiently. Amestejani compared two groups of 30 patients each who were adults

with an average age of 23.3 years. The authors did not report how the significant difference ($p < 0.05$) was calculated. However, the SCORAD scores were 24.8 ± 4.1 before treatment and 15.3 ± 3.1 after treatment with vitamin D, and 25.3 ± 5.2 before and 23.46 ± 4.2 in the placebo group.

Further studies are needed to determine the precise role of vitamin D in atopic dermatitis and particularly a sufficiently powered placebo-controlled randomised study.

4.3.2 Skin Cancer and Sun-Seeking Behaviour

There is a significant body of literature surrounding these subjects. It is an area of controversy, balancing on the one hand the need to limit sunlight exposure and skin cancer risk with the requirement for adequate sun exposure to obtain sufficient vitamin D levels.

In New Zealand, the National Institute for Water and Atmospheric Research (NIWA) uses the UV index to measure UV light intensity, and < 3 is low and > 10 is extreme. In the New Zealand summer the UV index is usually > 11 (extreme) at midday. In New Zealand in 2010, malignant melanoma was the sixth most common cause of death, accounting for 3.8% of cancer deaths with an age-adjusted rate per 100,000 of 43.4 in males and 36.1 in females (Māori and non-Māori combined) (208). New Zealand also has one of the highest age-standardised registration rates for melanoma in the world (209). The role of vitamin D in cutaneous carcinogenesis and melanoma has been recently reviewed and there is evidence that the vitamin D pathway may have a role in melanoma, as in-vitro 1,25 dihydroxyvitamin D inhibits tumour invasion and angiogenesis (210, 211). In a prospective cohort study by Newton-Bishop et al, higher levels of 25-hydroxyvitamin D were associated with lower Breslow thickness at diagnosis ($p = 0.002$) and were independently protective of relapse and death (212). In another study of melanomas by Nurnberg et al, significantly reduced 25-hydroxyvitamin D levels were found in stage IV (metastatic) patients, as compared with stage I patients (thin melanoma, no metastasis), while those with low 25-hydroxyvitamin D levels (< 25 nmol/l) developed earlier distant metastatic disease compared to those with levels > 50 nmol/l (213). These findings were supported by Gambichler et al who reported that decreased 25-hydroxyvitamin D was associated with increased tumour thickness and advanced tumour stage (214). Studies by Randerson-Moor et al and Major et al, in contrast, failed to show a relationship between 25-hydroxyvitamin D and melanoma (215, 216). However, Afzal et al found an association between higher levels of 25-hydroxyvitamin D and melanoma (217) when examining the hypothesis that elevated 25-hydroxyvitamin D is a surrogate maker for sun exposure, concluding that the absolute 20-year risk of melanoma was 1.5% in participants ≥ 60 years with winter 25-hydroxyvitamin D ≥ 50 nmol/l.

The role of vitamin D in non-melanoma skin cancer (squamous cell cancer and basal cell cancer) has attracted less study and the data are limited. Tang et al performed a nested case-control study and concluded that high 25-hydroxyvitamin D levels may be associated with a reduced risk of non-melanoma skin cancer (218). However, a study by Asgari et al suggested that higher prediagnostic 25-hydroxyvitamin D levels may be associated with an increased risk of subsequent basal cell carcinoma (219). Furthermore, Eide et al and Afzal et al found that increased 25-hydroxyvitamin D was significantly associated with an increased risk of non-melanoma skin cancer (217, 220).

Studies examining both patient and doctor understanding of sun protection, skin cancer and vitamin D show a mixed level of understanding and some confusion. A study from Queensland, Australia, of 2,001 residents reported that 21% had reduced their sun protection behaviour because of concern about vitamin D levels, and 32% thought a fair-skinned person needed at least 30 minutes in the sun per day between the hours of 10am and 3pm to maintain healthy vitamin D levels (221). In a further study from Brisbane of 2,867 urban office workers, 11% believed that sun protection might cause vitamin D deficiency and were less likely to use sunscreen (222). Using additional data from the Queensland report, it was concluded that media were the main source of information about vitamin D for 50% of the participants (223). In New Zealand, skin colour, rather than ethnicity, may be useful for communicating the risk-benefit of sun exposure (224).

Many New Zealand general practitioners (43% of a study of 1,089) were "not at all confident" about their vitamin D knowledge, leading to 10% recommending less sun protection all year (225). A similar study from Australia of 500 general practitioners showed a similar theme, with general practitioners offering advice that may increase their patients' risk of vitamin D insufficiency or skin cancer, and generally respondents expressed greater concern about vitamin D deficiency than about skin cancer (226).

In the face of contradictory literature, public and professional uncertainty, the New Zealand Ministry of Health has produced a consensus document on sun exposure and vitamin D. This document recognises that sun exposure is required for the general population for vitamin D synthesis. Noting that sunburn should always be avoided, sun protection between September and April is recommended, especially between 10am and 4pm, but in winter between May and August some midday sun exposure is recommended, such as a daily walk at noon with face, arms and hands exposed. There are caveats around those who are more likely to be vitamin D deficient and those who are at greater risk of skin cancer (90).

4.3.3 Vitiligo and Albinism

Vitiligo is usually an acquired disorder characterised by the development of circumscribed depigmented macules and patches. It affects approximately 0.5–2% of the population and can cause considerable psychological distress, especially in those with darker skin. Melanocytes disappear from involved skin and the pathogenesis is uncertain (1).

There are four studies that have examined the relationship of vitiligo and 25-hydroxyvitamin D status, and these are summarised in Table 11. 25-hydroxyvitamin D deficiency does exist in vitiligo patients but its direct relationship to the disorder is not known. Silverberg, in a case series of 45 patients with vitiligo, found very low 25-hydroxyvitamin D levels (defined as < 37.4 nmol/l) to be associated with comorbid autoimmune disease, with an OR = 10 but a wide confidence interval of 1.06–94.7, compared with those patients with vitiligo who did not have a comorbid autoimmune disease (227). Two studies from China are reported. Li et al examined VDR gene polymorphisms, vitiligo susceptibility and serum 25-hydroxyvitamin D. Using logistic regression comparing vitiligo patients and controls, with a cut-off level of 25-hydroxyvitamin D of greater than 46.7 nmol/l compared with less than 46.7 nmol/l, there was a reduced risk of vitiligo (adjusted OR 0.46; 95% CI: 0.28–0.75). VDR gene polymorphisms may affect 25-hydroxyvitamin D levels and the risk for development of vitiligo in a Chinese population. The variants *BsmI-B, ApaI-A* and *TaqI-t* allele were associated with a deceased risk of vitiligo and there is a dose-response relationship between deceased risk and increased 25-hydroxyvitamin D levels in individuals with *ApaI-A* allele (228). The other Chinese study,

from Xu et al, concluded that there was no correlation with 25-hydroxyvitamin D in the onset of vitiligo. However, this study report lacks detail and it is difficult to assess the conclusions (229). Saleh at al from Egypt concluded that patients with vitiligo had significantly lower 25-hydroxyvitamin D levels than a control group ($p < 0.001$) (230). It is likely however that those patients with vitiligo are more likely to cover their disease with clothing.

Albinism is a genetically inherited disorder of pigmentation resulting in reduced or absent melanin production (1). A study on albino children in South Africa concluded that albino children had a significantly higher 25-hydroxyvitamin D level than a control group at the same school. However, the p value given was 0.06 and statistical "outliers" were excluded. It is inferred that the "normally" pigmented children had dark skin (231).

Table 11: Studies of vitiligo and vitamin D

Author/date	Study type/country	Study population	Age (years)/sex	Conclusion
Silverberg 2010 (227)	Case series/USA	Hospital	Mean 22.6 Male (n = 24) Female (n = 21)	Very low 25-hydroxyvitamin D (<34.4 nmol/l in 13.3%) associated with comorbid autoimmune disease (OR10; 95% CI:1.06–94.7)
Li 2012 (228)	Case control/China	Hospital	Cases n = 749, Controls n = 763. Mean case 24.7 Mean controls 26.4 Cases: Male (n = 414) Female (n = 335) Controls: Male (n = 413) Female (n = 350)	Dose-response relationship between reduced risk of vitiligo and increased 25-hydroxyvitamin D levels in *Apa1-A* VDR carriers
Xu 2012 (229)	Case control/China	Hospital	Cases n = 171 Mean age not reported Male (n = 80) Female (n = 91) Control group: uncertain	No significant difference between patients and control (p value not reported)
Saleh 2013 (230)	Case-control/Egypt	Hospital	Cases n = 40 Controls: data not reported Mean 34.1 Male (n = 18) Female (n = 44)	Significant difference between patients (mean 30 nmol/l) and control (121.3 nmol/l) (p = 0.0001)

VDR = Vitamin D receptor.

4.3.4 Systemic Sclerosis

Systemic sclerosis, also known as scleroderma, is a condition of unknown aetiology that affects the skin, blood vessels and internal organs. The typical changes in the skin are of progressive fibrosis, leading to thickening and hardening of the skin. There are two major subtypes, limited and diffuse. In limited disease, fibrosis is confined usually to the fingers, hands, face and includes the CREST syndrome (calcinosis,

Raynaud's phenomenon, oesophageal reflux, sclerodactyly and telangectases). In diffuse disease, the fibrosis is more widespread. Morphea is a different and distinctive condition with localised areas of cutaneous fibrosis but no internal involvement. The common form is plaque-like but it can also be linear, inflammatory and rarely generalised morphea (1).

Several studies have examined systemic sclerosis and 25-hydroxyvitamin D. These are summarised in Table 12. Braun-Moscovici et al found 25-hydroxyvitamin D deficiency in a group of Mediterranean patients (defined as 25-hydroxyvitamin D ≤ 30 nmol/l) but no correlation was found between 25-hydroxyvitamin D status and disease duration or severity (232). In a large cross-sectional study from Northern France and Southern Italy, substantial insufficiency and deficiency was detected. A significant correlation was found between the European Disease Activity Score (a clinical assessment tool for scleroderma) and low 25-hydroxyvitamin D levels ($p = 0.04$) (233). Rios Fernandez reviewed 48 patients with systemic sclerosis, finding 25-hydroxyvitamin D deficiency (defined as < 75 nmol/l) in 81% and insufficiency (defined as < 25 nmol/l) in 9.5% (234). A larger study of 65 patients found deficiency (defined as < 25 nmol/l) in 29% and insufficiency (25–75 nmol/l) in 66% with a mean 25-hydroxyvitamin D level of 39.4± 22.7 nmol/l (235). Note that in these last two studies, the definitions of deficiency and insufficiency have been transposed.

Five case-control studies have been published. Matsuoka et al examined the 25- and 1, 25-dihydroxyvitamin D_3 levels in 19 patients and compared them with matched healthy controls (236) . Similar levels were observed in both patients and controls with no statistical difference (69.9 ± 7.5 nmol/l and 72.4 ± 7.5 nmol/l respectively, $p > 0.1$) and there was no correlation between skin area involved and vitamin D levels. Calzolari matched 60 patients and 60 controls and found that 25-hydroxyvitamin D levels were lower in the patients (median 23 nmol/l, range 7.4–229.6 nmol/l) compared with controls (97.3 nmol/l, range 34.9–344.4 nmol/l, $p < 0.001$). Furthermore, 65% had 25-hydroxyvitamin D levels below 75 nmol/l (237). However, no difference was noted between the 25-hydroxyvitamin D levels of 43 patients with scleroderma (45 ± 37.9 nmol/l) and 99 patients with osteoarthritis (43.2 ± 30 nmol/l) (238). A seasonal study of 25-hydroxyvitamin D values in patients with systemic sclerosis found that in winter insufficiency (25–75 nmol/l) was more common in the patients than in controls ($p < 0.001$). Deficiency (<25 nmol/l) was more common in summer among patients than controls ($p < 0.0001$) (239).The largest study published to date examined the sera of 327 European patients compared with 141 healthy controls (240) . The 25-hydroxyvitamin D level was significantly lower in the scleroderma group ($p < 0.001$) and there was an inverse relationship between skin involvement and 25-hydroxyvitamin D concentrations.

Table 12: Vitamin D and systemic sclerosis

Author	Study type/country	Age (years)/sex	Outcome mean (SD)
Braun-Moscovici 2008 (232)	Case series/Israel	Mean 55 Male (n = 9) Female (n = 51)	Deficiency 46% (< 30 nmol/l) Mean = 34.4 (± 18) nmol/l
Vacca 2009 (233)	Case series/France & Italy	Mean 57 Male (n = 14) Female (n = 142)	Insufficiency 84% (< 75 nmol/l) Deficiency 28% (< 25 nmol/l) Mean = 47.4 (± 27.5) nmol/l
Rios Fernandez 2010 (234)	Case series/Spain	Median 59.1 Male (n = 0) Female (n = 48)	Insufficiency 9.5% (< 25 nmol/l) Deficiency 81%(< 75 nmol/l) Mean not given
Caramaschi 2010 (235)	Case series/Italy	Mean 58.1 Male (n = 13) Female (n = 52)	Insufficiency 66% (75–25 nmol/l) Deficiency 29% (< 25 nmol/l) Mean = 39.4 (± 22.7) nmol/l
Matsuoka 1991 (236)	Case control/USA	Mean 51 Male (n = 4) Female (n = 15) Cases n = 19, controls n = 19	No significant difference in 25 or 1-, 25-dihydroxyvitamin D_3 levels (p > 0.1) Means: Patients = 69.9 (± 7.5) nmol/l Controls = 72.4 (± 7.5) nmol/l
Calzolari 2009 (237)	Case control/Italy	Mean age: Not reported Male Not reported Female Not reported Case n = 60, controls n = 60	Significantly lower 25-dihydroxyvitamin D in cases Medians: Patients = 57 nmol/l, Controls = 97 nmol/l, p < 0.001) Insufficiency 63% (≥25 and ≤50 nmol/l) Deficiency 7%(≤ 25 nmol/l)
Belloli 2011 (238)	Case control/Italy	Mean cases 61 Male (n = 1) Female (n = 42) Mean controls 65 Male (n = 8) Female (n = 91) Cases n = 43, controls n = 99	Insufficiency 51% (75–25 nmol/l) Deficiency 35% (< 25 nmol/l) No difference to controls (insufficiency p = 0.278, deficiency p = 0.334) Means Patients = 45.2 (± 37.9) nmol/l Controls = 43.2 (± 30) nmol/l
Seriolo 2011 (239)	Case control/Italy	Mean cases 58.5 Male (n = 0) Female (n = 53) Mean controls 59.9 Cases n = 53, controls n = 35	In winter: Insufficiency (75–25 nmol/l) 60% n = 32 case, n = 19 controls (p < 0.001) Deficiency (< 25 nmol/l) 9% n = 5 case, n = 4 controls (p value not reported). In summer: Insufficiency n = 34 cases, n = 18 controls (p < 0.001) Means: Patients = 54.2 (± 33.4) nmol/l Controls = 98.3 (± 38.4) nmol/l
Arnson 2011 (240)	Case control/Europe (Israel, Spain, Italy, Hungary)	Mean 56.7 Male Not reported Female Not reported Cases n = 327, controls n = 141	Significant difference between cases and controls Patients = 33.7 (± 22.5) nmol/l Controls = 53.9 (± 24.2) nmol/l (p < 0.001)

SD = Standard deviation.

4.3.5 Behçet's Disease

Behçet's disease is a multisystem disorder. The international study group for the diagnosis of Behçet's disease requires the major criterion of recurrent oral ulceration, and two minor criteria from recurrent genital ulceration, eye lesions, cutaneous lesions or a positive pathergy test (241). The cutaneous findings can include erythema nodosum, acral and facial sterile pustules, Sweet's syndrome-like lesions and pyoderma gangrenosum. Histologically, there is a neutrophilic angiocentric infiltrate with leucocytoclasis (early) or lymphocytic (late) vasculitis (1). One hundred and sixty patients with Behçet's disease, of which 102 were active, were compared with rheumatoid arthritis and multiple sclerosis patients (242). Decreased levels of 25-hydroxyvitamin D were found in the active Behçet's disease patients compared with the inactive stage and with the controls, mean (SD) 22.5 (± 14.2) nmol/l, 27.7 (± 12.9 nmol/l) and 35.0 (± 13.0) nmol/l respectively. A study from Turkey, where this disease is prevalent, compared 32 patients with Behçet's disease with 31 matched healthy controls (243). In patients with Behçet's disease, the 25-hydroxyvitamin D levels were significantly lower (mean 34.3, range 10.0–89.3 nmol/l) than the controls (mean 47.3, range 30.1–92.2 nmol/l, $p < 0.001$).

4.3.6 Miscellaneous Skin Diseases

There are a number of other publications around vitamin D and the skin. They can be broadly placed into three groups; vitamin D deficiency associated with photoprotection, vitamin D disease associations and heritable disease. They are summarised in Table 13.

Table 13: Other skin diseases

Vitamin D deficiency due to photoprotection	Vitamin D disease associations	Heritable disease
Xeroderma pigmentosum (244, 245) Gorlin syndrome (244) Organ transplant patients (246) Erythropoietic protoporphyria (247)	Ichthyosis (248, 249) Chemotherapy induced mucocutaneous toxicity (250) Pressure ulcers (251) Urticaria/angio-oedema (252, 253) HIV/Insulin lipoatrophy (254)	Vitamin D dependent Rickets type II (255)

Xeroderma pigmentosum is a rare autosomal recessive disorder caused by an inability to repair defective UV-induced DNA damage. These patients are at great risk of skin cancer and consequent early death. Gorlin syndrome is an autosomal dominant disorder caused by a mutation in the tumour suppressor gene PCTH resulting in the development of multiple basal cell carcinomas. Rigorous sun protection is mandatory in the routine management of these two disorders. Two studies reported levels of 25-hydroxyvitamin D_3 in patients with these diseases. Three patients with xeroderma pigmentosum and one patient with Gorlin syndrome were found to have reduced levels of 25-hydroxyvitamin D_3 compared with the authors' stated normal range of 37.4–224.6 nmol/l (244). In a larger study of 15 patients with xeroderma pigmentosum, 10 were found to have reduced 25-hydroxyvitamin D levels compared to the authors' stated normal range of 25–170 nmol/l, but no association was found between the level and duration of sun protection (245). Solid organ transplant patients are also routinely advised to take careful sun protection measures as prolonged immunosuppression impairs the ability to repair photodamage and increases the risk of skin cancer. In a case-control study, 31 renal transplant patients were found to have significantly lower 25-hydroxyvitamin D than their age- and gender-matched controls (246).

Similar photoprotection advice is given to patients with porphyrias. These are a diverse collection of diseases due to faults in the production of haemoglobin resulting in an accumulation of precursors which can cause photosensitivity. Porphyrias can be genetic or acquired. Erythropoietic protoporphyria, which is due to a deficiency of ferrochetalase resulting in excessive protoporphyrin IX, produces painful phototoxicity. Holme et al studied 201 patients with this disorder, finding 126 (63%) insufficient and 34 (17%) deficient in 25-hydroxyvitamin D (247).

Vitamin D abnormalities have been described in a variety of other skin diseases and usually deficiency is reported. These diseases include congenital ichthyosis, ichthyosiform erythroderma in children and adolescents with darker pigmented skin, chemotherapy induced mucocutaneous toxicity and dysgeusia, pressure ulcers in older ambulatory patients, urticarial/ angio-oedema and HIV/insulin and lipoatrophy (248-254).

Vitamin D-dependent rickets type II is a rare disorder due to a generalised resistance to 1, 25-dihydroxyvitamin D_3 because of mutations in the VDR gene. A variety of mutations can cause the disorder. However, a usual feature is hair loss. The VDR is expressed in the hair follicle. Patients with this disorder who have nonsense mutations that introduce premature stop signals, are totally hormone resistant and all have alopecia. It can therefore be inferred that the VDR is involved in hair growth (255).

4.3.7 Summary

Because it is not central to the aims of this thesis, the section “Other Skin Diseases and Vitamin D” has been brief and concise. The quality of studies varies but generally is low to moderate. The problem of the definition of acceptable values of vitamin D deficiency and insufficiency runs through these papers. Publication bias may also be an issue reporting only those results that show a difference.

4.4 Antimicrobial Peptides and Vitamin D

Antimicrobial peptides intersect with many aspects of skin disease and vitamin D. For example, atopic dermatitis and psoriasis are associated with abnormal antimicrobial peptide activity. This section discusses antimicrobial peptides and places them in context with the previously described skin diseases and vitamin D.

Antimicrobial peptides are mediators of cutaneous innate immunity and protect the skin primarily from microbial infections. The two important types are defensins and cathelicidins. The human genome contains only one cathelicidin gene, and cathelicidin is produced as a pro-peptide which is cleaved to form active LL-37, which itself can be further cleaved to form smaller peptides with differing functions (256). Vitamin D is an important regulator of cathelicidin expression through a vitamin D_3 response element in the promoter region of the cathelicidin gene (257, 258).

Cathelicidin and defensin expression is significantly reduced in acute and chronic lesions of atopic dermatitis compared with psoriasis. This relative deficiency may account for the susceptibility of patients with atopic dermatitis to infection (259). The administration of vitamin D_3 (cholecalciferol) 4,000 IU for 21 days significantly increased the cathelicidin expression in the lesions of atopic dermatitis (260). Cathelicidin and human β defensin 2 have higher expression in lesional psoriatic skin in vitamin D sufficient compared with vitamin D deficient patients (261). Narrowband UVB is a routine treatment for atopic dermatitis and psoriasis. In both psoriasis and atopic dermatitis, narrowband UVB has been demonstrated to increase cathelicidin levels, although it decreases levels of β-defensin 2 after six treatments in healing lesions, while at the same time increasing serum 25-hydroxyvitamin D levels to correct vitamin D_3 insufficiency (262). However, in a study of 12 patients with psoriasis who were given UVB supplemented by 20µg daily of cholecalciferol, there was no significant change in cathelicidin mRNA levels in patients with psoriasis comparing both pre- and post-UVB treatment, but there was a significant decrease in the healthy controls. Furthermore, defensin levels were significantly reduced in the psoriatic patients after UVB treatment (175). Ninety-three patients with psoriasis were compared with 50 controls in a study to evaluate the effect of narrowband UVB on vitamin D and cathelicidin levels. Before treatment, 25-hydroxyvitamin D levels were significantly lower in psoriatic patients (31.5 ± 14.41 nmol/l) compared with controls (53.5 ± 19.6 nmol/l, $p = 0.015$). However, serum cathelicidin levels were higher in psoriatic patients (13.24 ± 3.2 ng/ml) than in controls (7.92 ± 5.33 ng/ml, $p < 0.001$). After narrowband UVB, there was a significant elevation of 25-hydroxyvitamin D levels to 56.85 ± 5.2 nmol/L ($p < 0.001$) and an elevation of cathelicidin levels to 29.4 ± 4.2 ng/ml, $p < 0.02$) (263). It is interesting to note that topical calcipitriol also increases cathelicidin expression, but at the same time reduces the skin inflammation associated with psoriasis. There is an unexplained paradox in the mechanism of the pathogenesis of psoriasis in that extracellular DNA and RNA released from psoriatic cells, when complexed with cathelicidin, create a pro-inflammatory trigger mediated by interferon type 1 (α) production from plasmacytoid dendritic cells, so that anti-inflammatory treatments (narrowband UVB and calcipotriol) are associated with increased cathelicidin levels (264).

The Toll family are part of the innate immune system and are preserved through different species. In humans these receptors are called toll-like receptors and they can recognise antimicrobial ligands. The pivotal study of Liu et al reported the activation of human macrophages via toll-like receptors after exposure

to synthetic 19-kD *M tuberculosis* derived lipo-peptide, and found upregulation of the VDR gene and consequent induction of cathelicidin. Knowing that African-Americans, who have low 25-hydroxyvitamin D levels and who are recognised to have increased susceptibility to *M. tuberculosis,* the serum of these individuals was found to induce significantly less cathelicidin than Caucasians. Supplementing the African-American with 25-hydroxyvitamin D_3 restored toll-like receptor induction of cathelicidin (257). This paper provides a modern scientific validation of Niels Finsen's work described in Chapter 2, Section 2.2.2.1. High dose vitamin D has subsequently been shown to be beneficial in patients with pulmonary tuberculosis (265).

It is therefore interesting to speculate on the parallels between psoriasis, lupus and antimicrobial peptides. One model of psoriasis is that mechanical injury triggers cathelicidin production by keratinocytes, which complexes with self-DNA released from damaged cells. This complex triggers toll-like receptor mediated type 1 interferon production via plasmacytoid dendritic cells. Through interleukin production, a self-sustaining feedback mechanism is established leading to perpetuation of the psoriatic plaque (266). In cultured keratinocytes, narrowband UVB has been demonstrated to lead to membrane expression of selected nuclear antigens recognised by anti-La and anti-Ro 60 derived from patients with lupus erythematosus (126). This self-DNA could bind to cathelicidin, triggering toll-like receptor mediated type 1 interferon production via plasmacytoid dendritic cells. Nucleic acid can act as ligands for toll-like receptors and plasmacytoid dendritic cells have been found in close association with severely damaged keratinocytes in lupus (121, 267). Interferon type 1 production is important in the pathogenesis of lupus (268).

4.5 Cardiovascular Disease and Psoriasis

This section discusses the association of psoriasis as an independent risk factor for cardiovascular disease. It summarises the historical background, the possible mechanisms of the association and recent literature with an emphasis on the cross-sectional studies. The section is included because the ViDA study offered the opportunity to undertake a cross-sectional comparison of cardiovascular risk factors between psoriasis participants and the remainder of the ViDA patients.

4.5.1 History

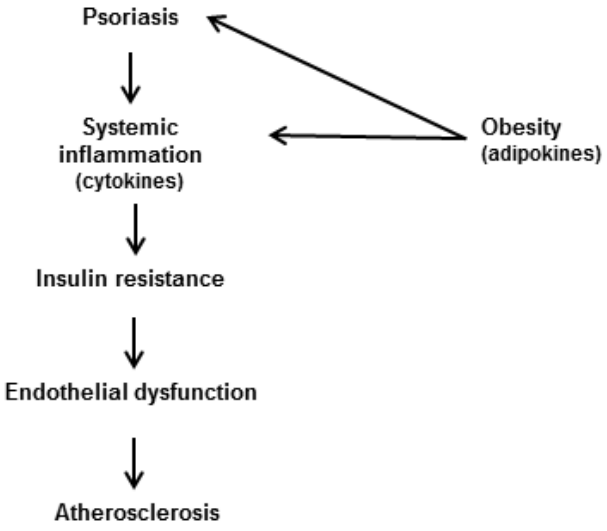
In 1961 Reed et al published a study of 86 patients with psoriasis and arthritis and the post-mortem findings in 16 of these patients. Five patients died of myocardial infarction and there was a moderate degree of arteriosclerosis in all. It was written that, "*The acute exudative nature of psoriasis may be merely a reflection of severe inflammation seen elsewhere in synovial membranes of the joints, iris, urethra, and the collagen-elastic tissues of the heart and aorta*" (269).

Subsequently, in 1973 Charles Mc Donald and Paul Calabresi wrote a letter that was published in the *New England Journal of Medicine* entitled, "Occlusive vascular disease in psoriatic patients". They examined the records of 253 consecutive patients with psoriasis and noted that 29 patients (11.5%) experienced one or more episodes of occlusive vascular disease, compared with 14 patients (5%) in an age-matched control group (270). Their observation was then formally reported in a retrospective case-control study of 323 patients with psoriasis and 325 age-matched controls who did not have psoriasis but did have other dermatological disease. The populations were stratified into those with and those without predisposition to occlusive vascular disease. In each group the occurrence of occlusive vascular disease was significantly higher ($p < 0.05$) in predisposed psoriatic patients compared with predisposed non-psoriatic patients. Extent of psoriasis, rather than duration, also predisposed to occlusive vascular disease, as did age over 50 years (271).

4.5.2 Mechanism of the Association of Cardiovascular Disease and Psoriasis

It is interesting to consider why psoriasis may be associated with increased cardiovascular risk. A useful concept is the "psoriatic march" first proposed by Griffiths in an editorial in *The Lancet* in 2007 (272) and then further discussed by Boehncke in 2011 (273). The concept proposes that psoriasis is a systemic inflammatory disease and through a progression of events results in atherogenesis. It is summarised in Figure 5.

Figure 5: The "Psoriatic March" adapted from *Boehncke et al, 2011* (273)



There are systemic biomarkers of inflammation that are raised in psoriasis and these include C-reactive protein, vascular endothelial growth factor and markers of platelet activation. There is also a complex relationship between psoriasis, obesity and the cytokines produced by fat cells called adipokines. Obesity associated with psoriasis may be the key link for diabetes risk and the metabolic syndrome. Leptin, for example, is an adipocyte-derived hormone which controls appetite, but also has an important role in acute and chronic inflammatory processes. Patients with severe psoriasis have significantly higher leptin and leptin receptor expression than those with moderate to mild disease. Adiponectin, which is also derived from adipocytes, is considered a beneficial cytokine as it has anti-inflammatory actions. Adiponectin levels are decreased in psoriasis compared with healthy controls (274). PASI scores are significantly correlated to insulin secretion and also resistin, which is an adipokine associated with insulin resistance (275). This same study did not find an association with PASI and vessel wall thickness, which is pertinent to the study described in Chapter 7.

Psoriasis, therefore, is a state of systemic chronic inflammation, with a complex relationship with obesity, associated with insulin resistance. Insulin resistance causes endothelial dysfunction by altering the balance of vasodilating and vasoconstricting factors including nitrous oxide, prostacyclin, endothelin1 and angiotensin 2. Once the normal physiological balance is impaired, the endothelial environment changes to one that favours atherogenesis. Atherogenesis results from leukocyte adhesion to the endothelium, smooth muscle growth, impaired coagulation, vascular inflammation and ultimately atherosclerotic plaque rupture. Atherogenesis is considered a systemic inflammatory disease and, even in the absence of psoriasis, in a patient with atheroma, there are similarities between the inflammatory markers of psoriasis and atherosclerosis (276, 277).

4.5.3 Cardiovascular Risk Factors, Lifestyle and Psoriasis

In the last 10 years there have been many papers published on the association of psoriasis and cardiovascular risk. This is a complex issue with many factors and confounding variables. A wide variety of studies have been performed including cohort, cross-sectional and case control. A comprehensive review is beyond the scope of this thesis. Instead, this section discusses the relationship that psoriasis has with

common cardiovascular risk factors and lifestyle, including a summary of the cross-sectional studies of cardiovascular risk factors in psoriatic populations, which was the design of the baseline ViDA data. It is not the mandate of this thesis to extensively review the common cardiovascular risk factors but it is pertinent to discuss them given the substudy described in Chapter 7.

4.5.3.1 Cardiovascular Risk Factors and Psoriasis

The common cardiovascular risk factors are comprehensively summarised in the Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (278). The major risk factors are smoking, hyperlipidaemia, diabetes mellitus, hypertension and obesity. The recommendations include moderation of lifestyle factors including smoking cessation, modifying diet, increasing physical activity and exercise, obesity management, optimisation of blood lipid profile (focusing on the measurement of non-fasting total cholesterol and high density lipoprotein [HDL]) and effective management of hypertension. The consensus recommendations also acknowledge the cardiovascular risk of chronic inflammatory disease and particularly discuss the increased risk associated with rheumatoid arthritis and SLE. It acknowledges that increased cardiovascular risk is "likely" for a broader range of inflammatory rheumatic disorders, mentioning psoriatic arthritis but not psoriasis specifically.

In 2004 Mallbris et al found that the overall risk of cardiovascular mortality in inpatients admitted with psoriasis was increased by 50% (standardised mortality ratio 1.52; 95% CI: 1.44–1.60) compared with the general population. Admission was taken as a surrogate for more severe psoriasis and, furthermore, the excess risk increased with increasing number of hospital admissions (279). An observational study published in 2009 examined the outpatient records of all patients with psoriasis between 1985 and 2005. The study identified 3,236 patients with psoriasis and 2,500 controls. In the psoriatic patients there was a higher prevalence of diabetes mellitus, hypertension and smoking. After controlling for these variables, there was found to be a higher risk of ischaemic heart disease (OR 1.86; 95% CI: 1.51–2.11), cerebrovascular disease (OR 1.70; 95% CI 1.33–2.17) and peripheral vascular disease (OR 1.98; 95% CI, 1.32–2.82) compared with controls (139).

Two descriptive and uncontrolled studies have reported the Framingham 10-year risk of cardiovascular events. Kimball et al reported the Framingham risk of 2,899 patients in phase 3 studies of the biologic agent ustekinumab for moderate to severe psoriasis. In one of the trials, full data were not recorded and therefore 903 patients were excluded. However, of the remainder, 371 of 1,996 (18.6%) were at high risk and 246 of 1,996 (12.3%) at intermediate risk of cardiovascular events. Some patients had untreated diabetes, hypertension and dyslipidaemia at baseline (280). The PASI is an objective measure of the severity of psoriasis. Fernandez-Torres reported the Framingham risk from a cohort of 395 patients derived from a hospital dermatology department. Eight patients (33.3%) with a PASI of greater than 10 (moderate/severe psoriasis) had an intermediate risk and two patients (8.3%) a high risk of cardiovascular events in the next 10 years (281).

A case-control study from Spain examined vitamin D levels and the metabolic syndrome in 46 patients compared with an age/sex-matched control group without psoriasis. Patients with psoriasis had significantly lower levels of 25-hydroxyvitamin D (76.1 v 81.9 nmol/l, p = 0.007) compared with the control group, and

psoriatic patients with metabolic syndrome had significantly lower levels of 25-hydroxyvitamin D compared with those without metabolic syndrome (60.1 ± 18.7 v 81.9 ± 22.2 nmol/l, p = 0.007) (282).

4.5.3.2 Cross-Sectional Studies of Cardiovascular Risk and Psoriasis

The cross-sectional studies reporting odd ratios for mild and severe psoriasis are summarised in Table 14.

Neiman et al (283) conducted a population-based study in the UK examining the General Practice Research database. Severe psoriasis was defined as those who had ever had a diagnosis of psoriasis as well as systemic therapy, and mild as those who had a diagnosis of psoriasis but without systemic treatment. Controls were selected from the same practices and start dates as psoriasis patients, and 127,706 patients with mild psoriasis and 3,854 with severe psoriasis were identified. Patients with mild psoriasis had a higher adjusted odds of diabetes, hypertension, hyperlipidaemia, obesity and smoking compared with controls. Patients with severe psoriasis had higher adjusted odds of diabetes, obesity, and smoking than controls.

Kimball et al (284) examined data from two US based health care claims databases, called IMS Health Integrated Claims Database and Market Scan Commercial Claims and Encounters Database. The data were used to identify patients with psoriasis by diagnostic codes with a 3:1 matching of non-psoriatic controls. Severe psoriasis was defined as having at least one systemic treatment during the observation period while all others were classed as mild, with 20,614 and 25,556 patients with psoriasis identified, respectively, from Market Scan and IMS Health. Odds for atherosclerosis, congestive heart failure, type 2 diabetes and peripheral vascular disease were ≥ 1.20 for psoriasis patients. Severe psoriasis was associated with a higher rate of cardiovascular disease or risk factors.

Yang et al (285) examined the Longitudinal Health Insurance Database 2000 from Taiwan's National Health Insurance programme, which enrolled 98% of all Taiwanese residents in 2007. Patients with psoriasis were identified who had received two or more diagnoses of psoriasis and they were matched 3:1 with non-psoriatic controls. Severe psoriasis was defined as those patients who had phototherapy or systemic treatment and 1,685 patients with psoriasis were identified. Patients with severe psoriasis had higher adjusted odds ratios of congestive heart failure, uncomplicated diabetes, hyperlipidaemia and hypertension compared with controls, whereas patients with mild psoriasis were more likely to have uncomplicated diabetes compared with controls. As a group, patients with psoriasis were more likely to have congestive heart failure, ischaemic heart disease, uncomplicated diabetes mellitus, complicated diabetes mellitus, hyperlipidaemia and hypertension than those without psoriasis.

Langan et al (286) examined The Health Improvement Network database in the UK which contains anonymised medical data on 3.4 million patients and is "broadly" representative of the UK population. Mild, moderate and severe psoriasis was identified as ≤ 2%, 3–10% or > 10% respectively of body surface area. The study compared 4,065 patients with psoriasis with 40,650 controls. There was a "dose-response" effect for severity of psoriasis in adjusted odds ratio of the metabolic syndrome. Furthermore, obesity, hypertriglyceridaemia and hyperglycaemia increased with disease severity.

Armstrong et al (287) examined the National Psoriasis Foundation data in the USA. Mild, moderate and severe psoriasis were defined as < 3%, 3–10% and > 10% body surface area (BSA) respectively and 5,211 patients were identified. Compared with mild to moderate psoriasis, patients with severe psoriasis had increased odds of diabetes and cardiovascular disease.

The weight of evidence is that moderate to severe psoriasis is an independent risk factor for cardiovascular disease. Some studies, however, show no increase in cardiovascular mortality. Stern published two papers. The first in 1988 was a 10-year prospective study of 1,380 patients enrolled in a phototherapy follow-up, and no increase in cardiovascular mortality was observed (288). The second study in 2011, following the same group, concluded that only patients with exceptionally severe psoriasis had an increased mortality, compared with the general population and with other patients with extensive but less severe psoriasis (289). A Dutch study in 2010 of 15,820 patients with psoriasis concluded that psoriasis was not a clinically relevant risk factor for ischaemic heart disease hospitalisations in the population (290). A study from Denmark in 2012 reported no differences between subjects, with and without psoriasis, in respect of cardiovascular risk factors. However, this study relied on patient recollection of the diagnosis of psoriasis (291). A study from the Mayo clinic, Rochester, published in 2013, concluded that psoriasis was not associated with cardiovascular risk (292).

The highest level of evidence published is a meta-analysis of 14 cohort studies (2). Increased cardiovascular risk was identified only in individuals with severe psoriasis (needing systemic therapy or hospital admission).The risk ratio in severe psoriatic patients, relative to the general population, was 1.37 (95% CI: 1.17–1.60) for cardiovascular mortality, 3.04 (95% CI: 0.65–14.35) for myocardial infarction and 1.59 (95% CI: 1.98–4.86) for cerebrovascular accident.

On balance, the weight of evidence is that moderate to severe psoriasis is an independent risk factor for cardiovascular disease.

Table 14: Summary of cross-sectional studies comparing the odds of having cardiovascular risk factors in patients with mild and severe psoriasis compared with controls

Author	Setting/time frame	Patient numbers/control	Risk factor/database	Odds (95% CI) Psoriasis severity* None	Mild	Severe
Neimann 2006 (283)	United Kingdom General Practice Research Database 1987–2002	n = 131,560 Case control 5:1	Diabetes Hypertension Hyperlipidaemia Smoking BMI (25–30) BMI (> 30)	1 1 1 1 1 1	1.13 (1.08,1.18) 1.03 (1.01,1.06) 1.16 (1.12,1.21) 1.31 (1.29,1.34) 1.12 (1.10,1.14) 1.27 (1.24,1.31)	1.62 (1.30,2.01) 1.00 (0.87,1.14) 1.04 (0.84,1.28) 1.31 (1.17,1.47) 1.27 (1.14,1.42) 1.79 (1.55,2.05)
Kimball 2008 (284)	United States Health care claims data - two sources MS IMS 2001–2002	MS n = 20,614 IMS n = 25,556 Case control 3:1	Diabetes (T2) MS IMS Hypertension MS IMS Hyperlipidaemia MS IMS All Obesity MS IMS IHD MS IMS	 1 1 1 1 1 1 1 	 1.15 (1.10,1.21) 1.19 (1.13,1.25) 1.11 (1.07,1.14) 1.16 (1.12,1.20) 1.18 (1.14,1.22) 1.24 (1.20,1.28) 1.56 (1.35,1.82) 1.42 (1.15,1.74) 1.16 (1.07,1.26) 1.14 (1.08,1.21)	 1.45 (1.31,1.60) 1.80 (1.63,1.99) 1.31 (1.22,1.42) 1.52 (1.41,1.63) 1.18 (1.09,1.27) 1.40 (1.30,1.50) 1.63 (1.19,2.23) 1.56 (0.99,2.44) 1.37 (1.17,1.61) 1.44 (1.28,1.62)
Yang 2011 (285)	Taiwan Taiwan National Health Insurance Programme 2006–2007	n = 1,685 Case control 3:1	Diabetes Hypertension Hyperlipidaemia IHD	1 1 1 1	1.55 (1.09,2.19) 1.28 (0.95,1.71) 1.06 (0.76,1.49) 1.04 (0.32,3.36)	1.33 (1.11,1.60) 1.23 (1.06,1.43) 1.32 (0.98,2.63) 1.61 (0.98,2.63)
Langan 2012 (286)	United Kingdom General Practice Database (The Health Improvement Network)	n = 4,900 Case control 10:1	Diabetes (T2) Hypertension Hypertriglyceridaemia BMI (25–30) BMI (30–<35) BMI (>35)	1 1 1 1 1 1	1.28 (1.11,1.48) 1.16 (1.06,1.28) 1.33 (1.21,1.46) 1.15 (1.02,1.30) 1.15 (1.02,1.30) 1.44 (1.24,1.67)	1.50 (1.14,1.98) 1.21 (0.98,1.49) 1.95 (1.62,2.34) 1.48 (1.11,1.96) 1.48 (1.11,1.96) 2.94 (2.17,4.01)
Armstrong 2012 (287)	United States National Psoriasis Foundation surveys 2003–2009, 2011	n = 5,604 Between psoriatic severity groups	Diabetes Hypertension Hyperlipidaemia Heart Disease	NA NA NA NA	1* 1* 1* 1*	1.50 (1.08,2.08) 1.13 (0.93,1.37) 0.95 (0.77,1.16) 1.50 (1.01,2.24)

Psoriasis Severity* – the definitions of “mild”, “moderate” and “severe” are described in Section 4.5.3.2. CI = Confidence interval, BMI = Body mass index, MS = Market Scan Commercial Claims and Encounters Database, IMS = IMS Health Integrated Claims Database, Diabetes (T2) = Type two diabetes mellitus, IHD = Ischaemic heart disease, NA = Not applicable. 1* = Mild/moderate psoriasis as comparator.

4.5.3.3 Lifestyle Cardiovascular Risk Factors and Psoriasis

Given the extensive literature about psoriasis and cardiovascular disease, little has been explicitly published about psoriasis, exercise or physiological variables in relation to the lifestyle cardiovascular risk.

Raychaudhuri found that the median percentage of involvement of psoriasis in 104 patients with psoriasis was 5% among those with a high exercise level compared with 10% in those without a regular schedule (293). In the Iowa Women's Health Study, those women taking regular physical activity were less likely to have psoriasis than those who did not (294). However, in a study of psoriasis, diabetes and hypertension derived from the Nurses' Health Study II, there was no difference between the exercise activity in the psoriatic and control groups (295).

Modifiable risk factors were investigated in a study of 65 patients recruited from a university dermatology clinic with 52 controls. The Godin Leisure-Time Exercise Questionnaire was used to assess the frequency of strenuous, moderate and mild exercise taken for more than 15 minutes in a typical week. No significant difference was found in exercise, as measured by this scoring system, between psoriatic patients and controls (296).

A further study was undertaken using data from the Nurses' Health Study II to specifically examine the association between physical activity and the risk of incident psoriasis. During 1991 and 2005, 1,026 incident cases of psoriasis were followed, and with adjustment for age, smoking and alcohol use, increasing physical activity was found to be inversely associated with the risk of psoriasis. The most physically active quintile of women had a lower multivariate relative risk of psoriasis (0.72; 95% CI 0.59–0.89; $p < 0.001$) compared with the least active quartile (297).

It is possible that physical activity may alter the risk of psoriasis by having a systemic anti-inflammatory effect. Given that atheroma is now regarded as a systemic inflammatory disease, physical activity may reduce the risk of developing other systemic inflammatory disorders. For example, brisk walking and vigorous exercise are associated with substantial reductions in the incidence of coronary events in women (298).

Sarli examined heart rate recovery in 50 patients with moderately severe psoriasis (PASI 10) and a control group of 32 healthy volunteers (299). Heart rate recovery is defined as the decrease in heart rate after exercise and is estimated by obtaining the heart rate at 1, 2, 3, 4 and 5 minutes during recovery. Patients and controls underwent a Bruce protocol stress test. There was a significant difference between the heart rate recovery in the psoriatic group, compared with the control group at 3, 4 and 5 minutes, with a slower recovery for the psoriatic group. The physiological relevance of this in the context of psoriasis is difficult to determine, although a reduced recovery rate has been reported as an independent risk factor for cardiovascular mortality (300). The altered heart rate recovery may be another signal of the greater cardiovascular risk to which these patients are exposed.

The lifestyle of patients with psoriasis was examined using physiological variables by Demirel (301). There were two groups, one of men and the other women. Each group was composed of 15 patients with psoriasis and 15 controls. The patients had moderately severe psoriasis with an average PASI of 13.3 in

the male and 11.2 in the female group. Overall, there was no difference between the control and psoriatic groups in both genders, apart from a statistically significant difference between the physical activity as measured by an accelerometer, with both the psoriatic groups being more active than controls (male p = 0.02, female p = 0.04). Other physiological variables that were measured included pulmonary function, BMI, body fat, skin fold thickness, resting metabolic rate, lean body mass and maximum volume of oxygen to produce energy, which is a measure of physical fitness.

4.5.4 Summary

Moderate to severe psoriasis is now generally accepted to be a significant independent risk factor for the development of cardiovascular disease. The most likely link is the sharing of common pathophysiological mechanisms especially the systemic inflammatory pathways. This association has not been examined in a New Zealand population.

4.6 Summary of Literature Review

The literature review has shown that vitamin D has a complex role in the physiology and pathophysiology of skin disease. The role of vitamin D is further complicated by the interaction of different skin types, geographic location, behavioural and social factors.

In New Zealand, how does a disease exacerbated by sunlight exposure, cutaneous lupus, differ in relationship to a disease improved by sunlight exposure, psoriasis, with regard to vitamin D? There are gaps in knowledge about cutaneous lupus, psoriasis and vitamin D that this thesis seeks to fill. There are explanations in evolutionary biology to account for the fact that New Zealanders with darker skin have low vitamin D levels. International studies show that people of coloured skin have a greater risk of lupus, with conflicting reports about the role of vitamin D, but largely noting an association with reduced vitamin D levels. Furthermore, Māori and Pacific in Auckland, New Zealand, have a greater risk of systemic lupus but it is not known if they have a greater prevalence of cutaneous lupus compared with the European population nor, if there is a greater prevalence of cutaneous lupus, whether this is related to vitamin D status or not. Chapter 5 of this thesis provides answers to these questions.

Psoriasis is a common disorder affecting many New Zealanders and there are many treatments. Oral vitamin D_3 (cholecalciferol), which is a safe and well tolerated treatment, has not been examined in detail after early reports of possible benefit with some of its analogues. Chapter 6 describes a randomised, placebo-controlled study of the effect of oral supplementation of calciferol in psoriasis with participants from the ViDA study. With large participant numbers in the ViDA study, an examination of the cardiovascular risk of New Zealand patients with psoriasis is therefore possible and is described in Chapter 7.

Chapter 5 Cutaneous Lupus and Vitamin D

5.1 Prelude

Two studies were undertaken in order to study vitamin D and cutaneous lupus. The first was needed to identify patients with cutaneous lupus in the CMDHB region. Once the patient pool was identified then the second study on cutaneous lupus and vitamin D levels could be undertaken.

The process of identification of the patients permitted a separate study on the prevalence of cutaneous lupus in the CMDHB population. Chapter 5 is therefore divided into two sections: “Prevalence of Cutaneous Lupus”, the prevalence study, and “Cutaneous Lupus and Vitamin D Status”, examining the association of cutaneous lupus and vitamin D levels.

5.2 Prevalence of Cutaneous Lupus

5.2.1 Introduction

This section describes a study to find the patients with cutaneous lupus and then to calculate the prevalence of cutaneous lupus in the CMDHB population. It is known that systemic lupus is more common in Māori and Pacific people and that lupus is more common in people of coloured skin. This has been discussed in Chapter 4. In addition, anecdotally, in the dermatology clinic, cutaneous lupus is seen more commonly in Māori and Pacific people compared with other populations. The unique mix of demographics in the CMDHB facilitates the formal examination of the prevalence of cutaneous lupus in this community. Therefore, the hypothesis that cutaneous lupus may be more prevalent in Māori and Pacific people compared with European people could be tested within this population.

The CMDHB serves an ethnically diverse population in specifically defined geographic borders in South Auckland (302). There are 23 potential ethnic groups including NZ Māori, Pacific (different islands identified), NZ European and Asian (mainly Chinese and Indian). Each person is assigned one ethnic group even if they are of mixed race. CMDHB has the highest number of Māori and Pacific peoples of any district health board in New Zealand.

It is usually impossible to identify every patient with a particular disease in the community. However, the technique of capture-recapture is a methodology that addresses this problem. Capture-recapture method in epidemiology is an attempt to estimate the actual population based on incomplete ascertainment using information from distinct but overlapping databases (303). The method is derived from animal ecology studies. To estimate the actual population of an animal, some are captured, marked and then released. Some, but not all, are then recaptured within the same area and then an estimate of the actual population can be determined. Medical databases, however, are often not completely independent of each other, which is an assumption of the capture-recapture technique when applied to ecological systems. This limitation can be overcome when applied to medical modelling by using a log-linear method which accounts for dependencies among multiple sources. The best fit of the data can be assessed using Akaike’s information criterion (304). An example of such a capture-recapture study examined the completeness of

cancer registration in Ontario, Canada using three sources; hospital discharge data and reports from cancer centres, pathology reports from hospital laboratories and death certificate data (305).

The National Health Index (NHI) number is a unique identifier that is assigned to every person who uses health and disability support services in New Zealand (306). This number is assigned to laboratory reports which allow reports on the same individual, from different laboratories and services, to be linked.

5.2.2 Aim

To determine the prevalence and ethnic distribution of cutaneous lupus in the CMDHB area by comparing the identified cases with the known population denominator demographics.

5.2.3 Method

Potential patients with cutaneous lupus were identified from multiple sources from both hospital and community. In South Auckland the sole provider of laboratory services in the community was Diagnostic Medlab up until 2009 and the hospital service has always been provided by the CMDHB laboratory services.

A clinical analyst for disease coding at CMDHB retrieved the hospital electronic records. The NHI numbers were obtained to identify all inpatients who had a discharge diagnosis of lupus from Middlemore hospital in the period 2000–2009 and all outpatients with a diagnosis of lupus from 2007 to 2009. These periods represented the complete period of electronic records. The histopathology departments of CMDHB and Diagnostic Medlab supplied histopathology reports of all patients with a diagnosis of lupus from the period 2000–2009.The biochemistry departments of CMDHB and Diagnostic Medlab supplied all positive Ro serology from 2007 to 2009. The departments of rheumatology and nephrology at CMDHB supplied their databases of all patients with a diagnosis of systemic lupus. For the purposes of the capture-recapture analysis, the databases were labelled CMDHBhisto (CMDHB histology 2000–2009), DMLhisto (Diagnostic Medlab histology 2000–2009), Dermopd (dermatology outpatient discharges 2007–2009), ID1 (inpatients discharged from Middlemore hospital 2000–2009), Rheumopd (rheumatology outpatient discharges 2007–2009), Rheumopd1 (rheumatology department database), OP1 (all outpatient discharges 2007–2009), Dermopd (dermatology outpatient discharges 2007–2009), Renaldb (renal department database), RoCMDHB (Ro database CMDHB 2007–2009) and RoDML (Ro database Diagnostic Medlab). There were a total of 10 databases examined. This is summarised in Table 15.

Table 15: NHI sources of patients with cutaneous lupus

Institution	Source	Code	Years covered
Middlemore Hospital	Inpatient discharge diagnoses	ID1	2000–2009
Middlemore Hospital	Outpatient records	OP1	2007–2009
Middlemore Hospital	Histopathology Department	CMDHBhisto	2000–2009
Diagnostic Medlab	Histopathology Department	DMLhisto	2000–2009
Middlemore Hospital	Biochemistry Department	RoCMDHB	2007–2009
Diagnostic Medlab	Biochemistry Department	RoDML	2007–2009
Middlemore Hospital	Rheumatology Department outpatient records	Rheumopd	2007–2009
Middlemore Hospital	Dermatology Department outpatient records	Dermopd	2007–2007
Middlemore Hospital	Rheumatology database	Rheumopd1	N/A
Middlemore Hospital	Renal database	Renaldb	N/A

ID1 = Inpatients discharged from Middlemore Hospital 2000–2009, OP1 = All outpatient discharges 2007–2009, CMDHBhisto = Counties Manukau District Health Board histology 2000–2009, DMLhisto = Diagnostic Medlab 2000–2009, RoCMDHB = Ro database Counties Manukau District Health Board 2007–2009, RoDML = Ro database Diagnostic Medlab 2007–2009, Rheumopd = Rheumatology outpatient discharges 2007–2009, Dermopd = Dermatology outpatient discharges 2007–2009, Rheumopd1 = Rheumatology department database, Renaldb = Renal department database.

All practicing dermatologists (private and public) in the Auckland region were contacted to volunteer possible patient details. Rheumatologists within CMDHB, private rheumatologists in the Auckland region as well as paediatric rheumatologists at the national children's hospital Starship were also contacted. All general practices in CMDHB were contacted via the general practice newsletter. The South Auckland Lupus Society, a patient-run organisation, was also contacted. A letter to their members informed them of the study giving contact details and these details were also published on the society's website.

The addresses of patients with possible cutaneous lupus were identified to confirm their residence in the CMDHB boundary. Where ambiguity existed about the address in relation to the exact CMDHB boundary, CMDHB elective services were used to definitively establish the residence location. Elective services routinely check all referrals to CMDHB to ensure that the patient is eligible for funded CMDHB services and have an accurate knowledge of the CMDHB geographic boundary.

The clinical records of all patients who may have had cutaneous lupus were examined to establish the diagnosis and ethnicity. If needed, further information was obtained by directly contacting the patient's general practitioner, specialist, practice nurse or receptionist. A number of patients were contacted by letter and invited to attend the dermatology clinic for examination and confirmation of the diagnosis. Care was taken to select only cases where there was clear recording of the rash of ACLE. Where the main type of lupus had another subtype associated with it, the principal, most clinically relevant type was examined in the analysis. Cases of cutaneous lupus were accepted if there was clear evidence of cutaneous lupus recorded by a reliable documented record (including history, examination, serology, histology) as judged by the researcher; a documented dermatology opinion; or histological evidence of cutaneous lupus.

A database was constructed in Excel to record the data including name, NHI, date of birth, current age, ethnicity, gender, smoking status, date of onset of lupus, type of cutaneous lupus, the presence or absence of systemic lupus and the different databases from which the patient was identified. Statistical analysis was undertaken using Statistical Package for the Social Sciences (SPSS) version 22 and relative risk was calculated by age stratification using the Mantel-Haenszel method using EpiInfo ^{TM} V3.5.1. The record of

the identification from different databases was used to undertake a capture-recapture analysis to estimate the number of unidentified cases in the community. Capture-recapture was calculated using log-linear models in *R* (version 2.14) (307).

The denominator population data for CMDHB area in 2009 were obtained from the CMDHB population data, available from the Population Health Team at CMDHB, and is summarised in Appendix 3 (308). All ethnicity was recorded from Concerto which is the CMDHB electronic records system. Ethnicity on Concerto is either self-reported or reported by the patient's general practitioner.

Antinuclear antibody (ANA) and extractable nuclear antibody (ENA) were measured by the Auckland District Health Board Laboratory, LabPLUS laboratory, by immunofluorescence using HEp-2000® and Luminex, (Diagnostic Solutions Ltd, Australia).

Independent ethics committee approval was obtained from Northern Y Ethics Committee (NYT/09/52/EXP) and the study was also approved by the CMDHB Clinical Board and the Maōri Research Review Committee.

5.2.4 Results

5.2.4.1 Patient Records Examined

Approximately 4,800 potential patient NHI numbers with cutaneous lupus were identified from the different databases, including 728 from inpatient discharge records at Middlemore hospital, 448 from outpatient records, 386 from histopathology (CMDHB and Diagnostic Medlab), 2,818 from positive Ro serology (CMDHB and Diagnostic Medlab) and 502 from the databases of the rheumatology and nephrology departments. The digital notes of any patient who may have cutaneous lupus were examined to establish the diagnosis. The exact number of patient records examined in detail was not recorded but is estimated to have exceeded 3,000.

A summary of the sources of the cases of cutaneous lupus is given in Table 16.

Table 16: A summary of the sources of cases of cutaneous lupus

Institution	Source	Code	Number of cases identified*
Middlemore Hospital	Inpatient discharge diagnoses	ID1	42
Middlemore Hospital	Outpatient records	OP1	63
Middlemore Hospital	Histopathology Department	CMDHBhisto	34
Diagnostic Medlab	Histopathology Department	DMLhisto	11
Middlemore Hospital	Biochemistry Department	RoCMDHB	6
Diagnostic Medlab	Biochemistry Department	RoDML	0
Middlemore Hospital	Rheumatology Department outpatient records	Rheumopd	35
Middlemore Hospital	Dermatology Department outpatient records	Dermopd	42
Middlemore Hospital	Rheumatology database	Rheumopd1	5
Middlemore Hospital	Renal database	Renaldb	13

ID1 = Inpatients discharged from Middlemore hospital 2000–2009, OP1 = All outpatient discharges 2007–2009, CMDHBhisto = Counties Manukau District Health Board histology 2000–2009, DMLhisto = Diagnostic Medlab 2000–2009, RoCMDHB = Ro database Counties Manukau District Health Board 2007–2009, RoDML = Ro database Diagnostic Medlab 2007–2009, Rheumopd = Rheumatology outpatient discharges 2007–2009, Dermopd = Dermatology outpatient discharges 2007–2009, Rheumopd1 = Rheumatology department database, Renaldb = Renal department database. * Total number > 145 due to overlap of cases between databases.

5.2.4.2 Demographic Data

A total of 145 patients with cutaneous lupus were confirmed. The average age (SD) was 43.6 (± 15.9) years with a range of 11 to 81 years. There were 22 males (15.2%) with an average age of 46.45 (± 21.5) years and 123 females (84.4%) with an average age of 43.1 (± 14.8) years. There was a significant difference between the numbers of female and male patients with cutaneous lupus ($\chi^2 = 66.01$, $p < 0.001$).

The distribution of ethnicity both individually and combined into groups is shown in Table 17. For the purposes of analysis, the NZ Māori /Pacific, all European and Asian/Indian groups were combined and this is shown in Table 18. This data represents the numerator value for the age-adjusted relative risk calculation. There are fewer NZ Māori /Pacific in the older age groups compared with the European group.

Table 17: Ethnicity distribution of cutaneous lupus patients in CMDHB (all ethnicities and combined ethnicity)

Ethnicity	Number	Percentage (n = 145)
NZ Māori	31	21.4
Pacific (all)	48	33.1
NZ Māori and Pacific combined	79	54.5
NZ European/Pakeha (all)	47	32.4
Asian (all)	8	5.5
Indian	11	7.6
Indian and Asian combined	19	13.1

Table 18: Distribution of CMDHB cutaneous lupus patients by age groups and ethnicity

Age group (years)	European	NZ Māori/Pacific	Asian/Indian	Total
0–19	1	7	3	11
20–39	11	33	4	48
40–59	16	33	11	60
60+	19	6	1	26
Total	47	79	19	145

5.2.4.3 Type of Cutaneous Lupus by Gender, Age Group and Ethnicity.

The type of lupus, gender and distribution within age group categories is shown in Table 19. In keeping with other autoimmune connective tissue diseases, there are more female than male cases. There were 53 cases of ACLE, 19 cases of SCLE and 66 cases of DLE. Tumid, chilblain and panniculitic lupus were far less common compared with the other three groups. No cases of drug-induced lupus were identified.

Table 19: Type of cutaneous lupus by gender, age and ethnicity in CMDHB

		ACLE	SCLE	DLE	Tumid	Chilblain	Panniculitic	Total
Gender	Male	7	3	9	1	0	2	22
	Female	46	16	57	2	1	1	123
Age group (years)	0–19	7	0	3	1	0	0	11
	20–39	19	3	23	2	0	1	48
	40–59	20	6	31	0	1	2	60
	60+	7	10	9	0	0	0	26
Ethnicity	Māori/Pacific	24	1	51	2	0	1	79
	European	17	16	12	0	0	2	47
	Indian/Asian	12	2	3	1	1	0	19
Total		53	19	66	3	1	3	145

ACLE = Acute cutaneous lupus, SCLE = Subacute cutaneous lupus, DLE = Discoid lupus.

5.2.4.4 Type of Cutaneous Lupus and ANA Positivity

The data were examined for the types of cutaneous lupus and ANA positivity and this is shown in Table 20. Most cases of ACLE were ANA positive but most cases of DLE were ANA negative. ANA status was missing in 12 cases.

Table 20: Type of cutaneous lupus and ANA status

Type of Cutaneous Lupus	ANA Status		Total (%)
	Negative (%)	Positive (%)	
ACLE	2 (4)	48 (96)	50
SCLE	5 (29.4)	12 (70.6)	17
DLE	38 (64.4)	21 (35.6)	59
Tumid	1 (33.3)	2 (66.6)	3
Chilblain	0 (0)	1 (100)	1
Panniculitic	2 (66.6)	1 (33.3)	3
Total	48	85	133

ANA = Antinuclear antibody, ACLE = Acute cutaneous lupus, SCLE = Subacute cutaneous lupus, DLE = Discoid lupus.

There is a significant difference between the ANA status of the DLE group compared with all other groups ($p < 0.001$).

5.2.4.5 Population of CMDHB 2009 by Age Group, Ethnicity and Gender

The following table shows the denominator data. Table 21 is a summary of the population by combined ethnicity, age group and gender of CMDHB in 2009.

Table 21: Summary of the denominator population of CMDHB by age group, ethnicity and gender (2009)

	Total population			Female			Male		
Age group (years)	**Māori/ Pacific**	**European**	**Indian/ Asian**	**Māori/ Pacific**	**European**	**Indian/ Asian**	**Māori/ Pacific**	**European**	**Indian/ Asian**
0–19	85,150	41,181	25,520	41,790	20,014	12,330	43,360	21,167	13,190
20–39	53,480	41,813	27,660	28,510	20,917	14,780	24,970	20,896	12,880
40–59	36,170	57,298	23,330	19,160	28,639	12,500	17,010	28,659	10,830
60+	12,370	42,249	7,720	6,700	22,554	4,090	5,670	19,695	3,630
Total	187,170	182,541	84,230	96,160	92,124	43,700	91,010	90,417	40,530

5.2.4.6 Prevalence

The total prevalence of cutaneous lupus per 100,000 (95% CI) was 42.2 (33.87–52.59) in Māori/Pacific, 22.55 (14.44–35.23) in Indian/Asian and 25.75 (19.36–34.23) in the European population of CMDHB. Table 22 shows the prevalence of all types of lupus per 100,000 of the population in CMDHB by age group.

Table 22: Prevalence of all types of cutaneous lupus per 100,000 by age group and ethnicity (denominator is the total population in each ethnic age group)

	Prevalence of cutaneous lupus per 100,000 population (95% CI)		
Age group (years)	**Māori/Pacific**	**European**	**Indian/Asian**
0–19	8.22 (3.98–16.97)	2.42 (0.43–13.75)	11.75 (4.00–34.56)
20–39	61.7 (43.94–86.64)	26.3 (14.69–47.1)	14.46 (5.62–37.18)
40–59	91.24 (64.98–128.1)	27.92 (17.19–45.36)	47.15 (26.33–84.41)
60+	48.5 (22.23–105.8)	44.97 (28.79–70.23)	12.95 (2.29–73.34)

CI = Confidence interval.

Table 23 shows the type of lupus per 100,000 of CMDHB population with DLE being particularly prevalent in Māori/Pacific in comparison with the European group.

Table 23: Type of lupus and ethnicity per 100,000 (95% confidence interval), denominator total population in each ethnic group of CMDHB

	Type of cutaneous lupus per 100,000 population (95% CI)					
Ethnicity	**ACLE**	**SCLE**	**DLE**	**Tumid**	**Chilblain**	**Panniculitic**
Māori/Pacific	12.82 (8.62–19.08)	0.53 (0.09–3.02)	27.24 (20.73–35.82)	1.06 (0.29–3.70)	0	0.53 (0.09–3.03)
European	9.31 (5.81–14.9)	8.77 (5.40–14.24)	6.57 (3.76–11.49)	0	0	1.10 (0.30–4.00)
Indian/Asian	14.25 (8.15–24.9)	2.37 (0.65–8.66)	3.56 (1.21–10.47)	1.19 (0.21–6.72)	1.19 (0.21–6.72)	0

CI = Confidence interval, ACLE = Acute cutaneous lupus, SCLE = Subacute cutaneous lupus, DLE = Discoid lupus.

5.2.4.7 Relative Risk of Cutaneous Lupus by Gender, Age and Ethnicity

Table 24 shows the unadjusted relative risk of cutaneous lupus in CMDHB by age and sex; however, ethnicity is adjusted for age and sex with the Mantel-Haenszel correction. Females have a significantly higher relative risk of cutaneous lupus in this population compared with males. The relative risk of cutaneous lupus increases with age. Māori/Pacific have a greater relative risk of all types of cutaneous lupus combined, compared with Europeans, and a particularly high relative risk of DLE. The trend of the

relative risk for SCLE is reversed, with the European population having a higher relative risk than Māori/Pacific but this does not reach statistical significance.

Table 24: Relative risk of cutaneous lupus by gender, age and ethnicity in CMDHB

		Relative risk (95% CI)			
Demographic		**All types lupus**	**ACLE**	**SCLE**	**DLE**
Sex	Female	1.66 (1.55–1.78)	1.70 (1.52–1.89)	1.65 (1.36–2.00)	1.69 (1.54–1.86)
	Male	1.00	1.00	1.00	1.00
Age (years)	0–19	1.00	1.00	1.00	1.00
	20–39	1.82 (1.61–2.05)	1.63 (1.29–2.06)	2.23 (2.23–2.24)	1.98 (1.72–2.27)
	40–59	1.94 (1.76–2.15)	1.70 (1.36–2.13)	2.3 (2.29–2.31)	2.10 (1.89–2.33)
	60+	2.41 (1.96–2.98)	1.72 (1.02–2.90)	3.44 (3.41–3.46)	2.58 (1.86–3.57)
Ethnicity*	Māori/Pacific	2.47 (1.67–3.67)	1.64 (0.84–3.18)	0.09 (0.01–1.1)	5.96 (3.06–11.6)
	Indian/Asian	1.01 (0.58–1.75)	1.60 (0.75–3.41)	0.39 (0.08–1.80)	0.61 (0.17–2.21)
	European	1.00	1.00	1.00	1.00

CI = Confidence interval, * adjusted for age and sex (Mantel-Haenszel). ACLE = Acute cutaneous lupus, SCLE = Subacute cutaneous lupus, DLE = Discoid lupus.

5.2.4.8 Capture-recapture Analysis

The eight databases that were considered the most comprehensive and used in the final capture-recapture models were CMDHB and Diagnostic Medlab histology and Ro serology, dermatology outpatient lupus discharges, outpatient discharges, rheumatology outpatient discharges and inpatient discharges from Middlemore hospital. A Poisson distribution was assumed and between-list dependence was modelled. Competing models, accounting for increasing complexity of between-list dependence were selected using chi-square statistics, plots of Pearson residuals and Akaike's information criterion.

Overlap in the first four lists, used in the capture-recapture, are depicted in the scaled rectangle diagram (Figure 6), with the largest square representing the total number of people identified with lupus during the study, and the smaller coloured rectangles having areas proportional to the number of people contained within them, along with the degree of overlap with other databases. The 88 subjects in the white space are people identified with lupus, but not in these four selected databases. The overlap in the second four lists is similarly depicted in the next scaled rectangle diagram (Figure 7).

Figure 6: Overlap in first four databases

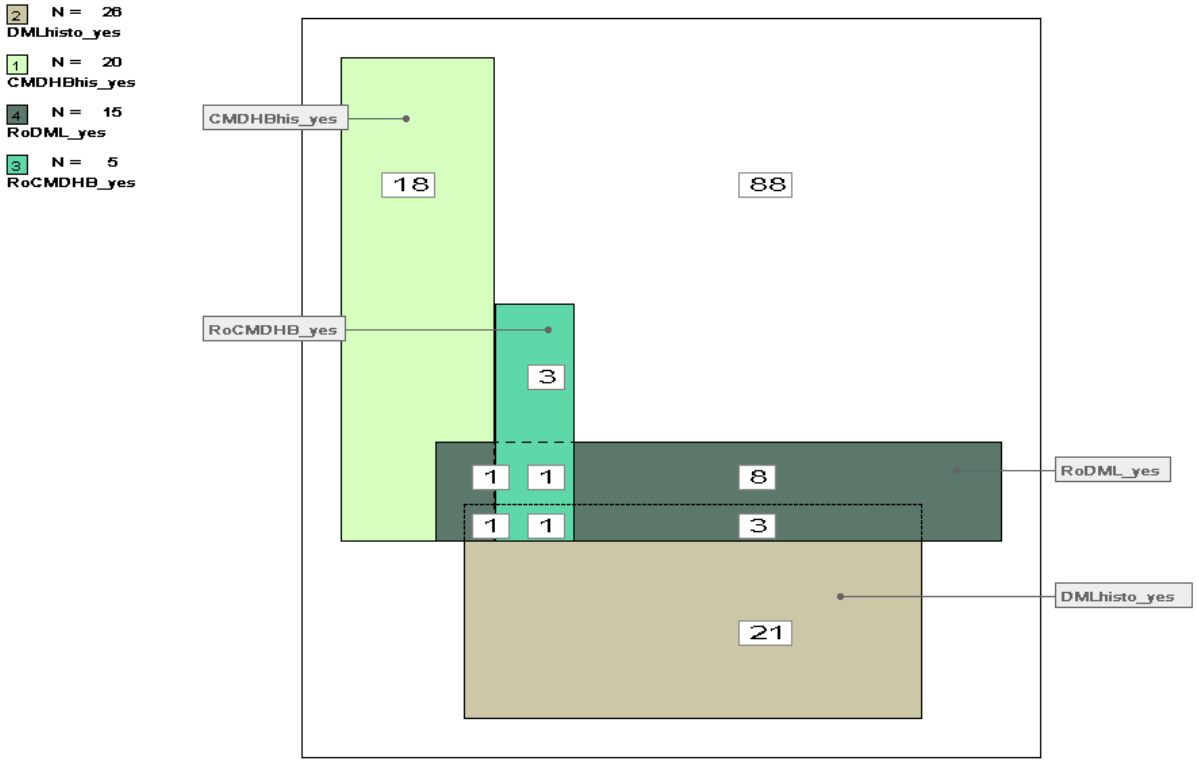
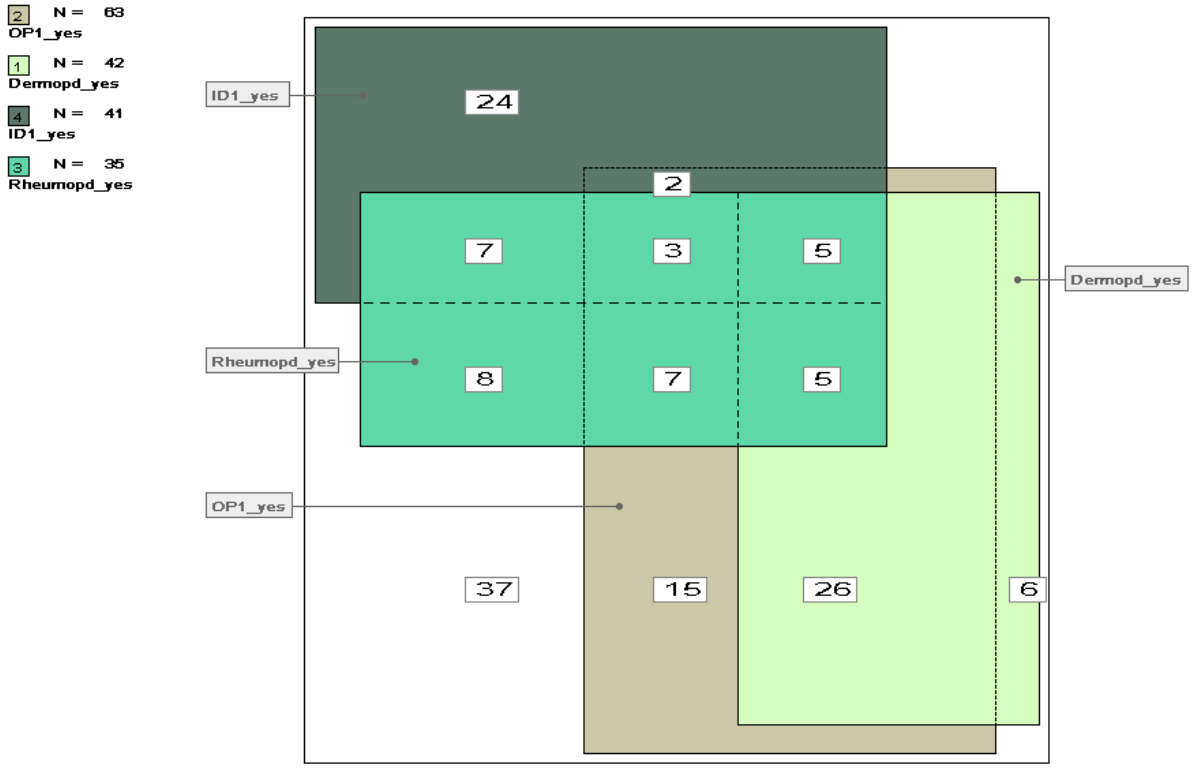


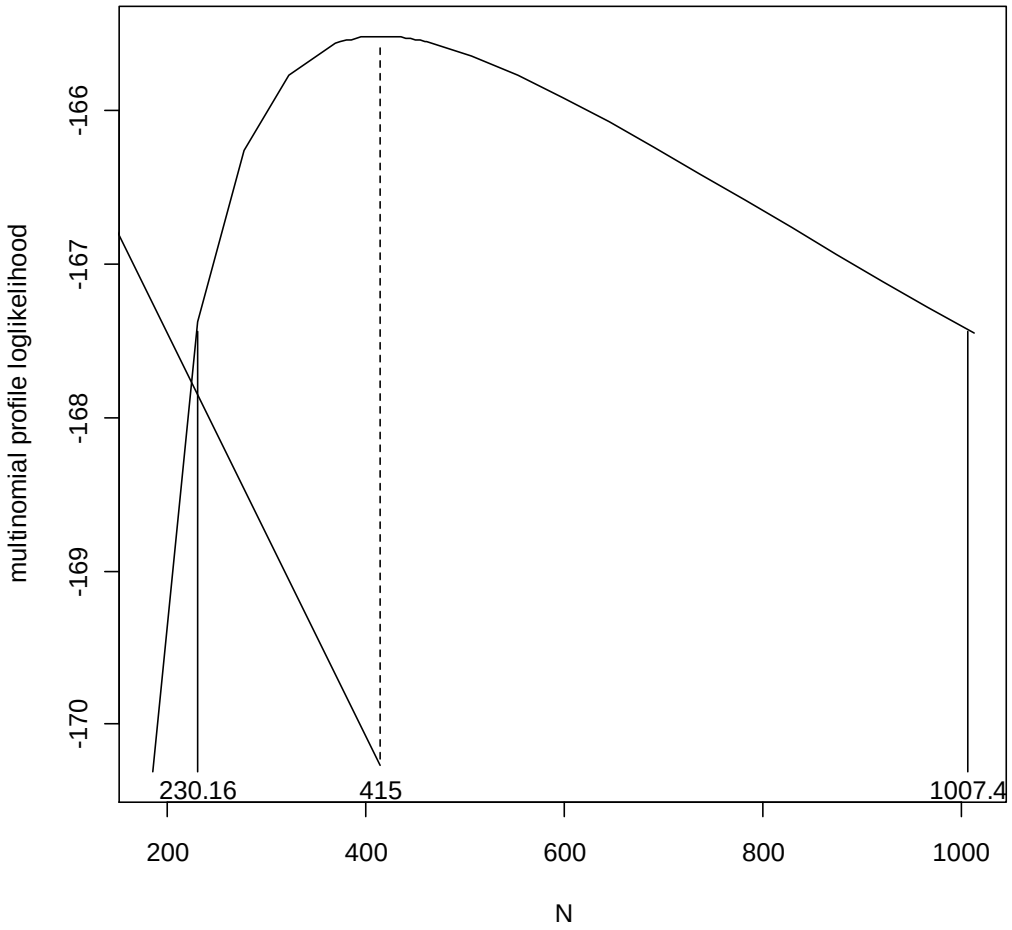
Figure 7: Overlap in second four lists



(CMDHBhisto = Counties Manukau District Health Board histology database, CMDHB histology, DMLhisto = Diagnostic Medlab histology database, RoCMDHB = Ro Counties Manukau District Health Board database, DermOPD = Dermatology outpatient database, OP1 = Outpatient database, RheumOPD = Rheumatology outpatient database, ID1 = Inpatient discharge database.)

The best fit was observed with a model (based on Akaike's information criterion) including two-way interactions between the eight lists included. The abundance of cases was 415 with a 95% profile likelihood confidence interval of 230 to 1,007 (Figure 8).

Figure 8: Profile Likelihood Confidence Interval



Using the estimated total population of CMDHB as 482,350 (Appendix 3) and the estimated total number of cutaneous lupus cases by capture-recapture (n = approximately 415), the estimated unadjusted prevalence of cutaneous lupus is 86.0 (95%CI: 78.1–94.7) per 100,000. This is much higher compared with 30.1 (95%CI: 25.5–35.4) per 100,000 based on the identified total of 145 cases.

5.2.5 Discussion

The prevalence of cutaneous lupus in a Māori/Pacific population has not previously been assessed in New Zealand. In the community served by CMDHB, the age/sex-adjusted relative risk of all types of cutaneous lupus is significantly higher in this population compared with the European population with a relative risk of 2.47 (95% CI: 1.67–3.67). Examining specific subtypes of cutaneous lupus shows no significant difference between these two population groups for ACLE, with an age/sex-adjusted relative risk of 1.64 (95% CI: 0.84–3.18). There is a trend, which just reaches significance, that SCLE age-adjusted relative risk is lower in the Māori/Pacific group compared with the European relative risk of 0.09 (95% CI: 0.01–1.1). There is a significant and marked increased relative risk, however, for DLE in Māori and Pacific compared with the European population, with an age/sex-adjusted relative risk of 5.95 (95% CI: 3.06–11.6). In keeping with many connective tissue diseases, women in the CMDHB population have a significantly higher risk of cutaneous lupus than males with a relative risk of 1.66 (95% CI: 1.55–1.78). Cutaneous lupus of all types generally affects older age groups (older than 40 years) more than younger age groups.

Cutaneous lupus is an uncommon disease in the CMDHB population. Per 100,000, the total prevalence was 42.2 (95% CI: 33.87–52.59) in Māori/Pacific, 22.5 (95% CI: 14.44–35.23) in Indian/Asian and 25.7 (95% CI: 19.36–34.23) in Europeans. The low prevalence is also reflected in the capture-recapture analysis which suggests an actual estimate of total cutaneous lupus cases in the CMDHB population of 415 but with a confidence interval of 230 to 1,007 (Figure 8), which compares with the 145 cases that were actually found in the study. The capture-recapture technique estimates the actual population to be 86.0 (95% CI: 78.1–94.7) per 100,000. Capture-recapture technique has not previously been used in the ascertainment of prevalence rate of cutaneous lupus. The technique has been used for the incidence rates of SLE in Allegheny County, Pennsylvania, which determined that the ascertainment-corrected incidence rate of SLE was 2.8 per 100,000 (95% CI: 2.6–3.2) (309).

ANA positivity was determined in the three groups of cutaneous lupus in this study. In a large community-based survey to determine the incidence and prevalence of SCLE in Sweden, ANA prevalences were also determined for SLE, SCLE and DLE. They were found to be SLE 81.8% (27 of 33 cases), SCLE 86% (13 of 19 cases) and DLE 33% (2 of 6 cases). These data are similar to those found in this study (ACLE 96%, SCLE 70.6%, DLE 33.6%) and provide a surrogate marker of consistency of case selection between the two studies.

The implications of these results are further discussed in Chapter 8.

5.3 Cutaneous Lupus and Vitamin D Status

5.3.1 Introduction

The different types of cutaneous lupus and the association of lupus with low 25-hydroxyvitamin D levels have been discussed at length in Chapter 4. This section of the thesis reports a study measuring 25-hydroxyvitamin D levels in patients with cutaneous lupus compared with a control group. In addition, it examines if the presence (activity and scarring) of cutaneous lupus is associated with altered 25-hydroxyvitamin D levels.

In order to assess cutaneous lupus, a validated scoring system should be used to objectively score the severity of the cutaneous lupus. Cutaneous lupus produces inflammation and in some subtypes subsequent scarring with resolution. Both the inflammation and scarring can be clinically assessed. The different types of cutaneous lupus share a common histological lichenoid pattern of inflammation. DLE is the type of lupus that commonly heals with scarring and this may be due to frequent involvement of the bulge area of the hair follicles where the stem cells reside (310). The cutaneous lupus erythematosus disease area and severity index (CLASI) is a validated measurement instrument for cutaneous lupus erythematosus (311). The CLASI consists of two scores, the first measuring disease activity and the second measuring the damage caused by the disease. Activity is assessed on the basis of erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss and non-scarring alopecia. Damage is scored on the basis of dyspigmentation and scarring, including scarring alopecia. If the dyspigmentation lasts more than 12 months, the dyspigmentation score is doubled as it is inferred to be permanent. Different anatomical areas are scored and the score calculated according to the worst affected lesion in that area for each sign. A validation exercise for the CLASI demonstrated an intra-class correlation coefficient for inter-rater reliability of 0.86 for the activity score (95% CI: 0.73–0.99) and of 0.92 for the damage score (95% CI: 0.85–1.00). The Spearman's score for inter-rater reliability for the activity score was 0.96 (95% CI: 0.89–1.00) and for the damage score 0.99 (95% CI: 0.97–1.00) (311). The author of this thesis attended the Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, USA in 2010 to learn the CLASI from Professor Victoria Werth who devised this scoring system.

Cutaneous lupus is a disorder that is exacerbated by light exposure. Experimental reproduction of cutaneous lupus can occur with both UVA and UVB, and approximately 53% of patients with induced cutaneous lupus react to both UVA and UVB, 33% to UVB only and 14% to UVA (111). Routine clinical advice is to protect patients from sunlight. Māori women and Pacific people have lower levels of 25-hydroxyvitamin D compared with their European counterparts (94) and the first study of this thesis has shown that Māori and Pacific people in the CMDHB population have a higher prevalence of cutaneous lupus. Table 5 summarises the literature about 25-hydroxyvitamin D deficiency and cutaneous lupus. There are many association studies between SLE and low 25-hydroxyvitamin D (128). The second study of this thesis sought to test the hypothesis that 25-hydroxyvitamin D levels may be low in patients with cutaneous lupus compared with controls. In addition, a CLASI score was taken at the time of measurement of 25-hydroxyvitamin D levels to assess if there is a correlation between CLASI scores and 25-hydroxyvitamin D levels. The study of Word et al reported no correlation between the CLASI scores and 25-hydroxyvitamin D

levels in either the African-American or Caucasian and Hispanic patients with cutaneous lupus but no data were published (118).

5.3.2 Aim

The primary aim of this study was to measure 25-hydroxyvitamin D levels in patients who have cutaneous lupus and to compare them with a control group. The secondary aim was to assess if cutaneous lupus activity and scarring, as measured by the CLASI, were related to 25-hydroxyvitamin D levels.

5.3.3 Method

All 145 patients in CMDHB with cutaneous lupus who were identified in the first study of this thesis were invited by letter to attend the dermatology clinic to undertake a full skin examination to determine their CLASI activity and damage score. At the time of the examination, blood was taken to measure serum 25-hydroxyvitamin D and PTH level.

The control group was derived from LabPLUS. LabPLUS, an IANZ (International Accreditation New Zealand) accredited medical laboratory, performed testing of all 25-hydroxyvitamin D levels in Auckland during the study period and approximately 1,800 tests were estimated to be performed each month. The raw control group data were obtained for exactly the same time period as the study group data acquisition period, which was from 25 January 2011 until 5 May 2011, so that seasonal variation in 25-hydroxyvitamin D levels between cases and controls was excluded as a confounding variable. The complete study was therefore undertaken during the New Zealand mid-summer and autumn. A total potential pool of 2,179 25-hydroxyvitamin D levels were obtained together with matched NHI, name, date of birth, gender and age. Each potential control patient's NHI was checked against the recorded address to make sure that the control patient lived within the Auckland region (36.84° south, 174.7° north) so latitude was excluded as a confounding variable and all patients living outside the Auckland region were excluded. The ethnicity of the control group as registered against the NHI was also recorded. After screening the NHI to check the address fell within the Auckland region, a total of 684 were removed. The control group data were pooled and anonymised for the purposes of analysis, giving a potential 1,495 controls.

The study was powered on the basis that of the 145 patients known, if 80 participated, the estimate of the mean 25-hydroxyvitamin D level would have a 95% confidence interval width of about 4.5 nmol/l. It was considered significant if the mean level (adjusted for time of year, ethnicity and age) of 25-hydroxyvitamin D in cutaneous lupus patients was more than 5 nmol/l lower than in controls. It was estimated that a difference of 3.2 nmol/l (5% level of significance, power 80%) could be determined between the cutaneous lupus patients and the control group. The magnitude of the difference in 25-hydroxyvitamin D levels between cases and controls was very sensitive to the number of cases and not sensitive to the number of controls. Univariate and multivariate statistical analysis of the data was undertaken using SPSS version 22.

All the 25-hydroxyvitamin D levels, both lupus and the community controls, were measured by automated immunoassay using a Diasorin Liaison analyser at LabPLUS. This method typically shows a between laboratory variation of 10% to 30% (data from external quality assurance scheme). This method showed a negative bias when compared with a gold standard of liquid chromatography mass spectrometry (LCMS) method (Canterbury Health Laboratories). The Liaison values were therefore corrected to align with LCMS

using the formula corrected 25-hydroxyvitamin D = (measured 25-hydroxyvitamin D x 1.12) + 13 nmol/l (personal communication, Associate Professor James Davidson, Clinical Head, Department of Chemical Pathology, LabPLUS, Auckland City Hospital). PTH was measured by an electrochemiluminescence immunoassay using the sandwich principle on an E170 modular platform, Roche, New Zealand.

The study received ethical approval by Northern X Regional Ethics Committee reference number NTX/10/10/102. The study was approved by the Counties Manukau Clinical Board and the Māori Research Review Committee.

5.3.4 Results

5.3.4.1 Case and Control Characteristics

Eighty patients with cutaneous lupus attended for review; ACLE n = 25 (31%), SCLE n = 15 (19%) DLE n = 38 (47.5%) and panniculitic n = 2 (2.5%). The type of lupus by ethnicity is recorded in Appendix 4. There was a potential pool of 1,495 controls and 1,333 were matched within 10-year age-bands.

The demographic data comparing the cases with the controls are summarised in Tables 25 and 26. There was no significant difference between gender or age group. There is a significant difference between the ethnicity with a relatively larger number of Europeans and fewer Māori and Pacific in the control compared with the case group.

Table 25: Summary of demographic data of cases of cutaneous lupus and controls

		Cases (%)	**Control (%)**	**p value****
Gender	Male	16 (20)	388 (26)	p = 0.23
	Female	64 (80)	1,107 (74)	
Ethnicity	European	43 (54)	1,172 (78.4)	p = < 0.001
	Pacific (all)	17 (21)	48 (3.2)	
	Māori	13 (16)	45 (3.0)	
	Indian	4 (5)	122 (8.2)	
	Asian (all)	3 (4)	108 (7.2)	
Age group	16–23	4 (5)	80 (6)	p = 0.54
	24–34	6 (7.5)	151 (11)	
	35–44	19 (24)	240 (18)	
	45–54	18 (22.5)	293 (22)	
	55–64	12 (15)	271 (20)	
	65–84	21 (26)	298 (22)*	
Total		80	1,333	

* Percentages do not total to 100 due to rounding. ** = Chi-square.

Table 26 summarises the frequency of cases and controls by ethnicity in each age group.

Table 26: Summary of age group and ethnicity of cases and controls

	Age group	European	Pacific (all)	Māori	Indian	Asian (all)	Total
Cases	16–23	0	1	1	0	2	4
	24–34	2	3	1	0	0	6
	35–44	9	5	4	0	1	19
	45–54	7	5	5	1	0	18
	55–64	6	3	2	1	0	12
	65–84	19	0	0	2	0	21
	Total	43	17	13	4	3	80
Controls	16–23	57	5	4	4	10	80
	24–34	92	8	6	30	15	151
	35–44	173	8	10	24	25	240
	45–54	231	9	10	23	20	293
	55–64	230	7	5	20	9	271
	65–84	253	8	6	12	19	298
	Total	1,036	45	41	113	98	1,333

A comparison of the 25-hydroxyvitamin D levels by ethnicity between cases and controls is summarised in Table 27. In the largest groups (European, Pacific and Māori), there was no statistical difference between the 25-hydroxyvitamin D levels. There were three Asian cases and 108 in the control group so the statistical significance in this comparison is uncertain.

Table 27: Mean 25-hydroxyvitamin D levels by ethnicity

	Mean 25-hydroxyvitamin D level [SD] (nmol/l)		p value*
Ethnicity	**Case**	**Control**	
European	94.8 (30.5)	97.4 (39.2)	0.67
Pacific (all)	71.1 (30.1)	70.4 (32.8)	0.94
Māori	80.3 (29.6)	85.5 (37.1)	0.65
Indian	84.0 (31.9)	57.5 (28.6)	0.07
Asian (all)	141.7 (54.3)	75.1 (40.8)	0.007
Total	88.6 (33.6)	91.3 (40.2)	0.56

*t test. SD = Standard deviation.

To examine how 25-hydroxyvitamin D levels differed between different ethnicities in the two groups an ANOVA was undertaken and this is summarised in Table 28. A significant difference was found in the 25-hydroxyvitamin D levels of the Pacific, Asian and Indian control group compared with the European group.

Table 28: Cases and controls ANOVA comparison of individual ethnicity and 25-hydroxyvitamin D

	Cases*			Controls**		
Comparison	**Mean difference nmol/l (95% CI)**	**Std error**	**p value**	**Mean difference nmol/l (95% CI)**	**Std error**	**p value**
European v NZ Māori	14.5 (−13.05,42.14)	9.87	0.58	12.0 (−4.05, 28.0)	5.65	0.23
European v Pacific	23.80 (−1.18,48.79)	8.94	0.07	27.1 (13.3, 40.8)	4.88	<0.001
European v Asian	−46.81 (−98.88,5.27)	18.63	0.10	22.3 (11.0, 33.6)	4.09	<0.001
European v Indian	10.86 (−34.72,56.45)	16.31	0.96	39.9 (32.1, 47.7)	2.83	<0.001

* Equal variance assumed (Levene statistic 1.01, p = 0.38). Post hoc analysis, Tukey HSD. ** Equal variances not assumed (Levene statistic 2.8, p = 0.025). Post hoc analysis, Games-Howell option CI = Confidence interval.

5.3.4.2 25-hydroxyvitamin D Status, Lupus and Ethnicity

A multiple linear regression analysis was undertaken using the 25-hydroxyvitamin D level as the continuous variable controlling for sex, age, case or control status and ethnicity. The results are summarised in Table 29 and show that Māori/Pacific and Indian/Asian are associated with lower 25-hydroxyvitamin D values when compared with the European ethnicity, adjusting for age and sex. However, being a case or control is not significantly associated with 25-hydroxyvitamin D values, adjusting for age and sex.

Table 29: Linear regression using 25-hydroxyvitamin D as the continuous outcome variable controlling for age, sex, case or control and ethnicity

	25-hydroxyvitamin D (nmol/l)	
Variable	**Coefficient estimate (95%CI)**	**p value**
Constant	96.1 (89.7,102.5)	<0.001
Age (years)	0.02 (−0.1,0.1)	0.65
Sex (female v male)	−0.81 (−5.1,3.5)	0.72
Māori/Pacific (v European)	−20.4 (−27.8,−13.0)	<0.001
Indian/Asian (v European)	−30.0 (−35.4,−24.6)	<0.001
Case/control	1.69 (−7.2,10.6)	0.71

CI = Confidence interval.

5.3.4.3 Multivariate Odds Ratio for Cutaneous Lupus

The data were examined to see if the increased risk for cutaneous lupus in Māori/Pacific in this study was maintained, given the results of the previous prevalence survey. Logistic regression was undertaken and two models examined with and without 25-hydroxyvitamin D levels and controlling for age, sex and ethnicity, given the results of the linear regression analysis. The logistic regression is summarised in Table

30 and shows that the addition of 25-hydroxyvitamin D does not alter the model and therefore the ethnic differences in 25-hydroxyvitamin D do not explain the ethnic differences in cutaneous lupus.

Table 30: Multivariate odds ratio of cutaneous lupus associated with vitamin D and demographic variables

	Model 1	**Model 2**
Variable	**Odds ratio (95% CI)**	**Odds ratio (95% CI)**
Māori/Pacific (v European)	9.6 (5.6,16.4)	9.9 (5.7, 17.2)
Indian/Asian (v European)	0.9 (0.4, 2.0)	0.9 (0.4, 2.2)
Age (years)	1.0 (1.0, 1.0)*	1.01 (1.0, 1.0)*
Sex (female v male)	0.7 (0.4, 1.2)	0.7 (0.4, 1.2)
25-hydroxyvitamin D (nmol/l)	-	1.00 (1.0, 1.0)*

* Rounding to 1 decimal place. CI = Confidence interval.

5.3.4.4 25-hydroxyvitamin D, Lupus Activity and Damage (CLASI) Scores

The descriptive statistics of the CLASI activity and damage scores are summarised in Table 31.

Table 31: Summary statistics of CLASI activity and damage scores

CLASI	**N**	**Minimum**	**Maximum**	**Mean**	**Std error mean**	**Std deviation mean**	**Median**	**Mode**
Activity	80	0	34	7.35	0.79	7.10	5	3.5
Damage	80	0	27	6.50	0.81	7.29	0	0

Std = Standard.

The distribution of the CLASI activity and damage scores is shown in Figures 9 and 10.

Figure 9: Histogram of CLASI activity distribution

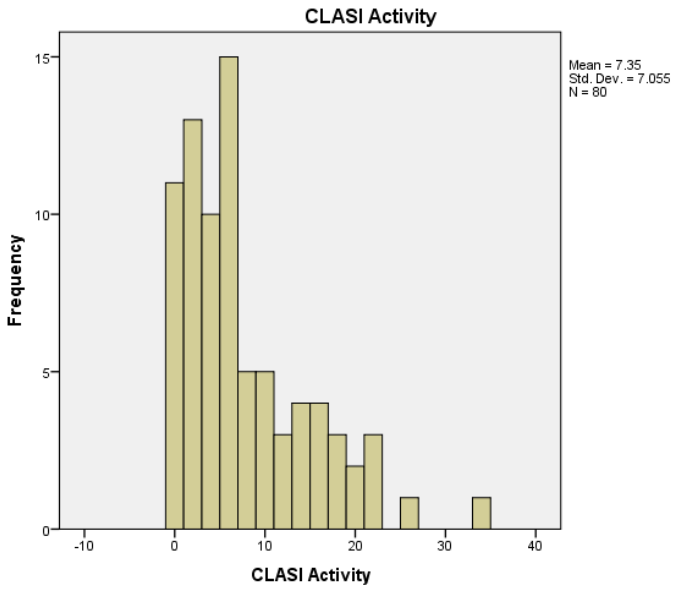
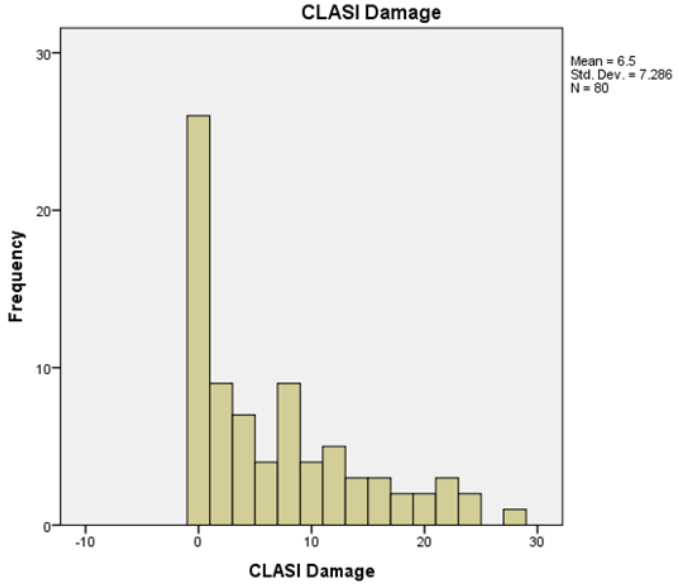


Figure 10: Histogram of CLASI damage distribution



The histograms of CLASI activity and damage show a positive skew with Kolmogogorov-Smirnov test for CLASI activity $p < 0.001$ and CLASI damage $p < 0.001$. To determine if the skew could be corrected, the scores were log transformed. Log transformation did not correct for the skew with Kolmogogorov-Smirnov test for CLASI activity $p = 0.04$ and for CLASI damage $p < 0.001$. Therefore, Spearman's correlation coefficient was determined for the correlation between the CLASI activity and damage scores $r_s = .402$ $p < 0.001$.

To examine if the CLASI scores (activity and damage) were significantly affected by 25-hydroxyvitamin D levels of the patients with cutaneous lupus, multiple linear regression was undertaken correcting for age, sex and ethnicity. The results of linear regression of CLASI activity and damage are summarised in Tables 32 and 33. Neither CLASI activity nor damage is associated with 25-hydroxyvitamin D levels after adjusting for demographic variables.

Table 32: Linear regression using 25-hydroxyvitamin D as a continuous outcome variable, CLASI activity and demographic variables as predictors

	25-hydroxyvitamin D (nmol/l)	
Variable	**Coefficient estimate (95%CI)**	**p value**
Constant	88.4 (55.5,121.2)	<0.001
Age (years)	0.13 (−0.4,0.6)	0.61
Sex (female v male)	−8.2 (−27.1,10.7)	0.39
Māori/Pacific (v European)	−18.6 (−36.1,−1.2)	0.04
Indian/Asian (v European)	14.6 (−12.5,41.8)	0.29
CLASI activity	0.10 (−0.9,1.1)	0.84

CLASI = Cutaneous lupus erythematosus disease area and severity index. CI = Confidence interval.

Table 33: Linear regression using 25-hydroxyvitamin D as a continuous outcome variable, CLASI damage and demographic variables as predictors

	25-hydroxyvitamin D (nmol/l)	
Variable	**Coefficient estimate (95%CI)**	**p value**
Constant	90.4 (58.4,122.5)	<0.001
Age (years)	0.13 (−0.39,0.65)	0.63
Sex (female v male)	−8.6 (−27.4,10.2)	0.36
Māori/Pacific (v European)	−17.7 (−35.9,0.4)	0.05
Indian/Asian (v European)	15.1 (−12.2,42.3)	0.27
CLASI damage	−0.2 (−1.3,0.8)	0.69

CLASI = Cutaneous lupus erythematosus disease area and severity index. CI = Confidence interval.

5.3.4.5 Analysis of 25-hydroxyvitamin D and Parathyroid Levels in Cutaneous Lupus

The interaction of the 25-hydroxyvitamin D level and the PTH was assessed. The mean (SD) PTH level was 4.49 (± 3.9) pmol/l (n = 79) and the normal range was 1.7–7.3 pmol/l. The distribution of the PTH and 25-hydroxyvitamin D levels was skewed with a significant Kolmogorov-Smirnov test for the PTH distribution ($p < 0.001$) and vitamin D levels ($p < 0.001$). The scores were log transformed but this failed to restore normality. Therefore, Spearman's correlation coefficient was determined between the PTH and the 25-hydroxyvitamin D level $r_s = -.144$ $p = .206$.

5.3.5 Discussion

The primary aim of this second study was to assess if there was a relationship between the presence of cutaneous lupus and 25-hydroxyvitamin D levels compared with a large control group. An unadjusted analysis of the 25-hydroxyvitamin D levels showed no difference between the lupus cases and controls. Linear regression was performed using 25-hydroxyvitamin D as a continuous variable and 25-hydroxyvitamin D level was found not to be significantly associated with cutaneous lupus when adjusting for age, sex and ethnicity (β = 1.69 [95% CI −7.2,10.6] p = 0.71) Table 29.

The secondary aim of the study was to examine if the severity of cutaneous lupus (activity and scarring), as measured by the CLASI, was related to 25-hydroxyvitamin D levels. This was assessed with linear regression and both activity and scarring were not related to 25-hydroxyvitamin D levels with CLASI activity (β = 0.10 [95% CI −0.9, 1.1] p = 0.84, Table 32) and CLASI damage (β = −0.21 [95%CI −1.3, 0.8], p = 0.69, Table 33).

There are many publications attempting to associate global (as opposed to only cutaneous) disease activity of SLE, as measured by differing parameters, and 25-hydroxyvitamin D levels. A review of 24 observational studies of 25-hydroxyvitamin D status and SLE showed that only 5 of 24 studies did not demonstrate an association of 25-hydroxyvitamin D and a disease parameter of SLE. The disease parameters measured

included the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), European Consensus Lupus Activity Measurement (ECLAM), Physician Global Assessment (PGA), British Isles Lupus Assessment Group (BILAG) and various biological markers including ANA and interferon activity (128). In this study, all types of cutaneous lupus were included in the assessment which makes the assumption that the underlying processes in the pathogenesis are the same, even if the clinical features are different.

The data of this second thesis study were examined to see if the relationship between lupus and ethnicity was upheld from the first study of the thesis. Despite the relative lack of Māori/Pacific participants compared with those of European ethnicity and the participants being derived from the cohort identified in the prevalence study, ethnicity remains a strong risk factor for cutaneous lupus with an adjusted odds ratio of 9.6 (95% CI 5.6,16.4) in Māori/Pacific compared with the European group (Table 30). If vitamin D level is added to the logistic regression model, the odds ratio in Māori/Pacific does not greatly change at 9.9 (95% CI 5.7, 17.2) and in this model 25-hydroxyvitamin D level did not have a significant odds ratio 1.00 (95% CI 1.0, 1.0, Table 30). It is interesting to speculate why there is the differing ethnic risk. This study would suggest that 25-hydroxyvitamin D is not an important risk factor so other genetic or environmental factors may be important. Perhaps genetics are the greater risk, given the common evolutionary ancestry of Māori and Pacific people but sharing the same environment as European New Zealanders.

There was a significant association between the CLASI activity and damage scores ($r_s = .402$ $p < 0.001$). This association is intuitively understandable as significant cutaneous lupus (especially DLE) would be associated with significant scarring. However, it also infers that the two processes go hand in hand as a reflection of the chronicity of the disease. Scarring DLE formed the largest subtype of cutaneous lupus and is most likely to scar.

There was no association between the 25-hydroxyvitamin D and PTH level ($r_s = -.144$ $p = .206$) which may be due to the small size. Alternatively, this may reflect the complex relationship between the two variables with many factors influencing the two, as discussed in Chapter 3, Section 3.1.3. The relevance and concentration of 25-hydroxyvitamin D at a cellular level may be different from that measured systemically.

The control group was large. It consisted mostly of European (78.4%) but very few Indian/Asian (15.4%) and Māori/Pacific (6.2%). There were significant differences in the 25-hydroxyvitamin D levels between the different ethnic groups. However, all the average 25-hydroxyvitamin D levels were in the normal range with European having the highest average level (97.4 nmol/l), then Māori (85.5 nmol/l) and the lowest being in Indian (57.5 nmol/l) (Table 27). The study was undertaken during summer and early autumn when levels of 25-hydroxyvitamin D would have been expected to be optimal. The differences between the ethnic groups was significant, with the European population having significantly higher 25-hydroxyvitamin D levels compared with Pacific, Asian and Indian (Table 28). The distribution of 25-hydroxyvitamin D levels is consistent with Bolland et al when the seasonal variation in 25-hydroxyvitamin D levels in 21,987 subjects was assessed in Auckland (94). Therefore, it is reassuring that the control group used in this study is consistent with a previously described group from Auckland. The finding of the 2008/09 New Zealand Adult Nutrition Survey was that the overall annual mean of 25-hydroxyvitamin D for New Zealand adults was 63.0 nmol/l. The mean level of 25-hydroxyvitamin D for Māori men was 60.9 nmol/l and for Māori women 57.2 nmol/l; for Pacific peoples, the mean was 49.6 nmol/l for men and 46.0 nmol/l for women. There were not

enough people of Asian ethnicity who provided blood to enable reliable estimates in this ethnic group. For those New Zealanders living in the most economically deprived areas, the mean level was 56.6 nmol/l. New Zealanders living in northern district health boards (including Auckland) had higher levels of 25-hydroxyvitamin D than those in southern DHBs (91).

The population group of this second thesis study was mainly European (54%) with a smaller number of Māori/Pacific (37%). The prevalence study described in Chapter 5 showed that cutaneous lupus is more prevalent among the Māori/Pacific population. Therefore, there was a recruitment bias in this study towards the European population. Thus, the patients who are most likely to have higher 25-hydroxyvitamin D levels but less likely to have cutaneous lupus dominated the sample and this may have biased the results. The control group for this study was selected from concurrent 25-hydroxyvitamin D levels taken from the wider Auckland community so that seasonal variation was eliminated as a confounding variable. It was not known why the individuals in the control group had their 25-hydroxyvitamin D levels measured or any co-morbidity that may have altered the value. The advantage of this control group however was the large numbers. Funding did not permit a nested case-controlled study using otherwise healthy age- and sex-matched controls.

The implications of these results are further discussed in Chapter 8.

5.4 Summary

Chapter 5 of the thesis consists of two sections.

The “Prevalence of Cutaneous Lupus” was a retrospective study of patient records. It shows that cutaneous lupus is an uncommon disease which is more prevalent in Māori/Pacific compared with the European population in CMDHB. DLE is especially prevalent among Māori/Pacific. A total of 145 cases of cutaneous lupus were identified in the CMDHB population. However, using the capture-recapture technique suggests the true total may be in the order of 415 cases but there is a wide confidence interval which reflects the rarity of the disease.

“Cutaneous Lupus and 25-hydroxyvitamin D Status” was a cross-sectional study of 25-hydroxyvitamin D in the patients with cutaneous lupus who were identified in the prevalence study and who agreed to participate. No association was found between 25-hydroxyvitamin D levels in those with cutaneous lupus compared with the control group. Furthermore, there was no association between the activity of cutaneous lupus and 25-hydroxyvitamin D levels. Māori/Pacific ethnicities are at particular risk for cutaneous lupus despite the recruitment bias towards the European population.

Chapter 6 Psoriasis and Vitamin D

6.1 Introduction

This chapter describes the methods, results and conclusions of a substudy of the ViDA study examining the effects of vitamin D supplementation on the severity of psoriasis.

6.1.1 The Vitamin D Assessment Study (ViDA)

ViDA was a double-blind, randomised, controlled trial assessing the effect of vitamin D_3 (cholecalciferol) 200,000 IU oral capsule at baseline, then 100,000 IU oral capsule monthly for up to four years, compared with a placebo capsule of sunflower lecithin manufactured by Tishcon Corporation (Westbury, New York, USA). The study assessed the effect of vitamin D supplementation on cardiovascular and respiratory disease event rates in older adults and the incidence of non-vertebral fractures. ViDA is registered with the Australian New Zealand Clinical Trials registry (Trial identification number ACTRN12611000402943) and was funded by the Health Research Council of New Zealand and the Accident Compensation Corporation. It had ethics committee approval from the Multi-Region Ethics Committee in 2010 (MEC/09/10/2010).

The primary outcome is the incidence rate of fatal and non-fatal cardiovascular disease, as assessed by mortality, hospital discharges and consultations with family doctors. The secondary outcomes are the incidence rates of respiratory disease, non-vertebral fractures and falls, as assessed by mortality, hospital discharges and self-reported questionnaires.

The inclusion criteria were:

- age 50–84 years (both male and female)
- ability to give informed consent
- resident in Auckland, New Zealand at recruitment
- anticipated residence in New Zealand for the four-year study period.

The exclusion criteria were:

- current use of vitamin D supplements (600 IU per day if aged 50–70 years; > 800 IU per day if aged 71–84 years)
- diagnosis of psychiatric disorders that would limit ability to comply with the study protocol, i.e., history of regular exacerbation of major psychosis (schizophrenia, bipolar disorder) in the last two years
- history of hypercalcaemia, nephrolithiasis, sarcoidosis, parathyroid disease or gastric bypass surgery
- enrolled in another study which would affect participation in the vitamin D study
- serum calcium from baseline sample > 2.50 mmol/l.

Participants were recruited from patient registers of general practitioners in Auckland and the target sample size was 5,100 participants. Patients were identified electronically and their contact details extracted from

patient registers. A personalised letter (n = 47,905) was sent to the home of each potential participant, along with the participant information sheet (ethics committee approved) and a one-page form to enter details and mail back to the study team in a pre-addressed envelope. Those who replied (n = 8,688) were phoned at home and if interested and eligible (n = 5,107) were given an appointment for a baseline assessment at the School of Population Health, The University of Auckland. An additional 143 eligible participants were recruited directly from community groups, giving a total of 5,250 who had baseline assessments.

After the baseline evaluation, participants were mailed a "run-in" questionnaire with a placebo capsule. They were only randomised if they returned their run-in questionnaire within four weeks (confirming taking of the capsule) and if their adjusted calcium (a baseline investigation) was ≤ 2.50 mmol/l. After excluding 140 potential participants who did not meet both criteria, 5,110 participants were recruited.

At the baseline assessment, the following data were collected from each person:

- Written informed consent
- Eligibility confirmed
- Contact details
- Current medication
- Past medical history
- Lifestyle including sun exposure, smoking, physical activity
- Blood pressure
- Arterial waveform measured by the Pulsecor R6.5B oscillometric device (Auckland, New Zealand) (312)
- Anthropometry
- Muscle strength
- Gait and balance
- Blood sample (to measure serum calcium with remaining serum alliquoted and stored at −80°C)

Patients were randomised within ethnic and 5-year age categories and random assignment was made to one of two treatment groups with block sizes of 8, 10 or 12. All treatment allocation was done automatically and the study personnel were blinded to the allocated group.

The oral capsules of vitamin D_3 or placebo were mailed to the participants' homes. The first mail-out contained two capsules (200,000 IU bolus) and then thereafter, monthly mail-outs sent 2.5mg (100,000IU) of vitamin D_3 or placebo until June 2013. Then for financial reasons, four capsules were mailed every four months with monthly reminders to take the capsules (letter or email) for the rest of the duration of the study.

Compliance was monitored by questionnaires being mailed to the participants' homes (monthly up to November 2013 and then four-monthly from March 2014), with a box to tick to indicate that the participant had taken the monthly capsule and if not to state the reason.

The 100,000 IU dose was chosen as it approximates to 3,300 IU per day which is required to raise 25-hydroxyvitamin D to 80–100 nmol/l. This level has been shown by some observational studies to be optimal

for health (87, 88, 313) with a minimum desirable level between 70 and 80 nmol/l (see Chapter 3, Section 3.1.3).

6.1.2 Psoriasis Substudy of the ViDA Study

The ViDA study offered the opportunity to study the effect of vitamin D_3 supplementation on patients with psoriasis. Randomised controlled studies of psoriasis produce strong treatment effects and require only small sample sizes. Psoriasis affects approximately 1–2% of the population so in a study recruiting 5,000 participants it would be expected that 50 to 100 of the participants would have psoriasis.

There are a number of validated tools to assess psoriasis and quality of life for patients with skin disease. The Dermatology Life Quality Index (DLQI) is a simple, validated and widely used questionnaire to assess the quality of life for patients with dermatological disorders (314). It is a 10-point questionnaire with a minimum score of 0 (no impairment to the quality of life) to a maximum of 30 and is completed by the patient (see Appendix 6). The Psoriasis Disability Index (PDI) is a validated and simple measure of the functional lifestyle disability produced by psoriasis (315). It is a 15-point questionnaire available as a tick box method or a visual analogue scale. The tick box method has a minimum score of 0 (no functional disability) to a maximum of 45 and is completed by patients with psoriasis (see Appendix 7). The PASI is a widely used scoring system to assign a number to the severity of psoriasis. It is an objective score completed by assessors rather than patients. The PASI combines the severity of the psoriasis (measured by erythema, induration and desquamation) and the percentage of area affected. The PASI can be easily calculated by online scoring tools including the PASI Calculator (316). The PASI has a minimum score of 0 (no psoriasis) and a maximum of 72.0. A 50% reduction in the severity of the PASI score can be considered as a clinically significant endpoint (317). A Physician Global Assessment (PGA) is an empiric measure of the severity of the psoriasis as scored by the assessor. The psoriasis substudy was approved by the New Zealand Multi-Region Ethics Committee on 19 April 2011.

6.1.2.1 Aim

The primary outcome of the psoriasis substudy was to determine if vitamin D_3 supplementation (100,000 IU per month) reduces the severity of psoriasis compared with placebo. The psoriasis severity was measured by the PASI and PGA. The secondary outcome was to determine if there was a change in the quality of life as measured by the DLQI and PDI.

6.2 Method

6.2.1 Participants and Assessment Protocol

All participants of the main ViDA study who answered “YES” to a question in the baseline questionnaire, *“Have you ever been told by a doctor that you have psoriasis?”* were invited to participate in the psoriasis substudy and were given a patient information form.

The inclusion criteria for participation on the psoriasis substudy were:

- answered “YES” at the main study baseline interview to the question, *“Have you ever been told by a doctor that you have psoriasis?”* and *“Have you had psoriasis in the last 12 months?”*

- provided informed consent to the psoriasis substudy
- willing to attend the study clinic for additional visits.

All potential participants for the psoriasis substudy were assessed prior to randomisation to confirm that they had psoriasis and then three further assessments were undertaken over a 12 month period as summarised in Table 34 (see Appendix 8 for "Initial visit" and "Follow-up visit" questionnaires).

Table 34: Schedule of visits for psoriasis substudy

	Visit 1 (Pre-randomisation)	**Visit 2 (3 months)**	**Visit 3 (6 Months)**	**Visit 4 (12 months)**
Eligibility	√			
Participant information form	√			
Informed consent	√			
Assessments; • History and examination • DLQI • PDI • PASI • PGA	 √ √ √ √ √ √	 √ √ √ √ √ √	 √ √ √ √ √ √	 √ √ √ √ √ √

DLQI = Dermatology Life Quality Index, PDI = Psoriasis Disability Index, PASI = Psoriasis Area Severity Index, PGA = Physician's Global Assessment.

All assessments were conducted by the investigator (Paul Jarrett) who completed PASI training using PASI training calculator (found at www.pasitraining.com) consistently obtaining correct scores of > 90% to ensure internal consistency. The results were tabulated onto an Excel spreadsheet for analysis.

At baseline and at the subsequent follow-up visits, participants were asked about their general medication and note was taken of any potential drugs that could alter psoriasis behaviour (lithium, systemic steroids, interferon, antimalarials, non-steroidal anti-inflammatories and tetracyclines) and specifically if the medication for their psoriasis had changed. There was no restriction placed on changing the psoriasis medication if that was required clinically.

To account for any change in treatment as a confounder in the final analysis, the following grading system was used at each follow-up assessment:

- 0 = No change in treatment
- 1 = Mild (weak) change in treatment
- 2 = Significant (strong) change in treatment

"Mild" was defined as a change in potency of topical treatment and "Significant" would be phototherapy or systemic therapy for psoriasis or a change in dosing of systemic therapy. These changes could be either positive (increase in treatment) or negative (decrease in treatment).

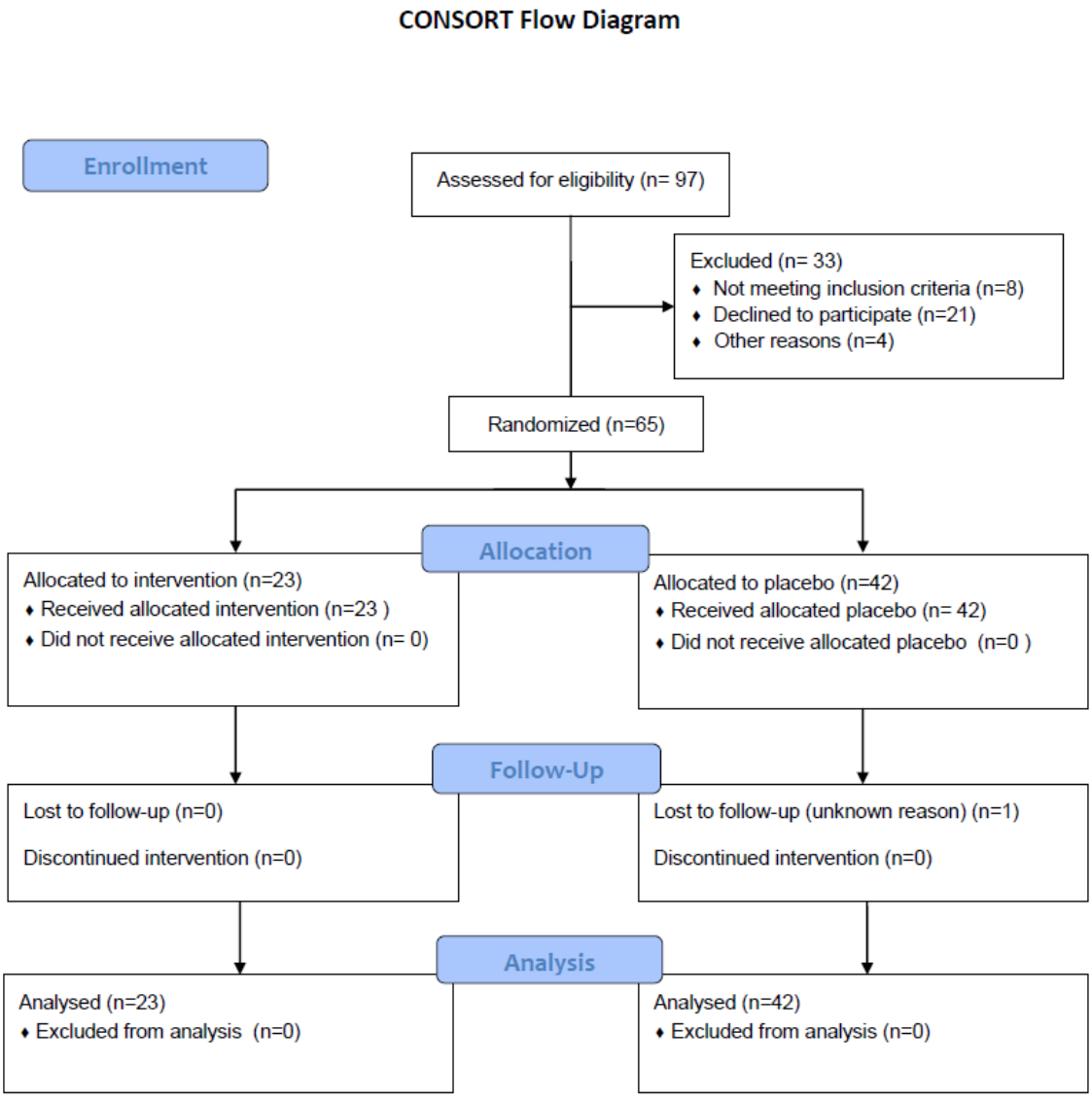
A sample size of 50 participants with psoriasis would have an 80% power to detect an effect of 0.5 in the PASI score and DLQI. The analyses were conducted on an intention-to-treat basis and those patients who were lost to follow-up were categorised as "missing data". The linear mixed model method was used to examine the outcome variables and statistical analysis was performed by SPSS version 22.

6.3 Results

6.3.1 Consort Flow Diagram

The Consort flow diagram summarises the enrolment, allocation, follow-up and analysis and is summarised in Figure 11. Participants were recruited between June 2011 and December 2012. Unblinding of the randomisation allocation coding for the psoriasis substudy occurred in July 2015 after the completion of the ViDA study.

Figure 11: Consort flow diagram for ViDA psoriasis substudy



6.3.2 Baseline Comparison of the Placebo and Vitamin D_3 Groups

The baseline characteristics of the vitamin D_3 and placebo group are summarised in Table 35. All patients had chronic, stable, plaque psoriasis. The two groups were unevenly numbered; however, there was no significant difference at baseline between the age, gender, ethnic groups, or duration of psoriasis. Of those who noted a seasonal deterioration in their psoriasis, most reported that it was worse in winter 73% (n = 19), in contrast to summer 23% (n = 6) and spring 4% (n = 1). Furthermore, there was no difference

between skin type or average sun exposure and the baseline dependent variables (PASI, PGA, PDI and DLQI) showed no significant difference between the two groups. None of the patients was identified as taking additional, over the counter vitamin D supplements on review of their drug history.

Table 35: Baseline comparison between placebo and vitamin D_3 groups

	Placebo	**Vitamin D_3**	**p value**
Number (%)	42 (65)	23 (35)	
Age (years) (SD)	64.7 (± 7.4)	68.4 (± 8.7)	0.07*
Gender (%)			
Female	17 (40)	8 (35)	
Male	25 (60)	15 (65)	0.65**
Ethnic groups (%)			
European	38 (90)	22 (96)	
Māori	2 (5)	0 (0)	
Pacific	2 (5)	0 (0)	
Asian	0 (0)	1 (4)	0.29***
Duration of psoriasis (years) (SD)	25.2 (± 16)	28.6 (± 19.0)	0.44*
Seasonal deterioration in psoriasis (%)			
Yes	22 (52)	6 (26)	
No	20 (48)	17 (74)	0.09**
Winter or summer deterioration in psoriasis (%)			
N	19	6	
Summer	4 (21)	2 (33)	
Winter	15 (79)	4 (67)	0.61***
Fitzpatrick skin type (%)			
1	1 (2)	0 (0)	
2	8 (19)	5 (22)	
3	20 (48)	14 (61)	
4	10 (24)	3 (13)	
5	3 (7)	1 (4)	0.82***
Average week day outdoors sun exposure (0–6 hours)			
0	5 (12)	7 (30)	
1	21 (50)	5 (22)	
2	10 (24)	10 (43)	
3	1 (2)	1 (4)	
4	1 (2)	0 (0)	
5	3 (7)	0 (0)	
6	1 (2)[A]	0 (0)[A]	0.06***
Average weekend outdoors sun exposure (0–7 hours)			
0	3 (7)	4 (18)	
1	11 (26)	5 (23)	
2	8 (19)	8 (36)	
3	10 (24)	5 (23)	
4	5 (12)	0 (0)	
5	2 (5)	0 (0)	
6	2 (5)	0 (0)	
7	1 (2)	0 (0)[B]	0.34***
PASI [SD]	3.0 [± 2.1]	3.3 [± 3.8]	0.69*
PGA [SD]	1.6 [± 0.8]	1.7 [± 1.1]	0.75*
PDI [SD]	2.8 [± 4.1]	3.3 [± 4.1]	0.60*
DLQI [SD]	3.7 [± 4.6]	2.2 [± 2.2]	0.14*

PASI = Psoriasis Area and Severity Index, PGA = Physicians Global Assessment, PDI = Psoriasis Disability Index, DLQI = Dermatology Life quality Index. SD = Standard deviation. * t test, ** $\chi 2$, *** Fisher's exact test. [A] Percentages do not equal 100 due to rounding. [B] One response missing so N = 22.

6.3.3 Correlation of the Assessments

To investigate consistency in the assessments and for internal validation, correlations were examined between the baseline PASI and PGA, completed by the investigator, as well as between the baseline DLQI and PDI, completed by the participant, at baseline. These correlations test consistency of the assessment by the investigator and the participants. Correlation was also undertaken for the baseline scores between

the investigator and the participant to examine if the investigator's assessment of the psoriasis matched that of the participant. The distribution of the baseline measured variables was skewed with significant Kolmogorov-Smirnov tests (PGA $p < 0.001$, PASI $p = 0.008$, PDI $p < 0.001$, DLQI $p < 0.001$); therefore Spearman's correlation coefficient was calculated. There was a significant correlation between all the scores demonstrating good investigator consistency and correlation between the investigator and participants' assessment of their psoriasis. The correlations are summarised In Table 36.

Table 36: Intra-investigator/participant and inter-investigator/participant correlations for baseline assessments

Assessment	Correlation	Spearman's rho	p value
Intra-investigator	PASI/PGA	0.81	<0.001
Intra-participant	DLQI/PDI	0.72	<0.001
Inter-investigator and participant	PASI/DLQI	0.34	0.005
	PASI/PDI	0.44	<0.001
	PGA/DLQI	0.30	0.02
	PGA/PDI	0.44	<0.001

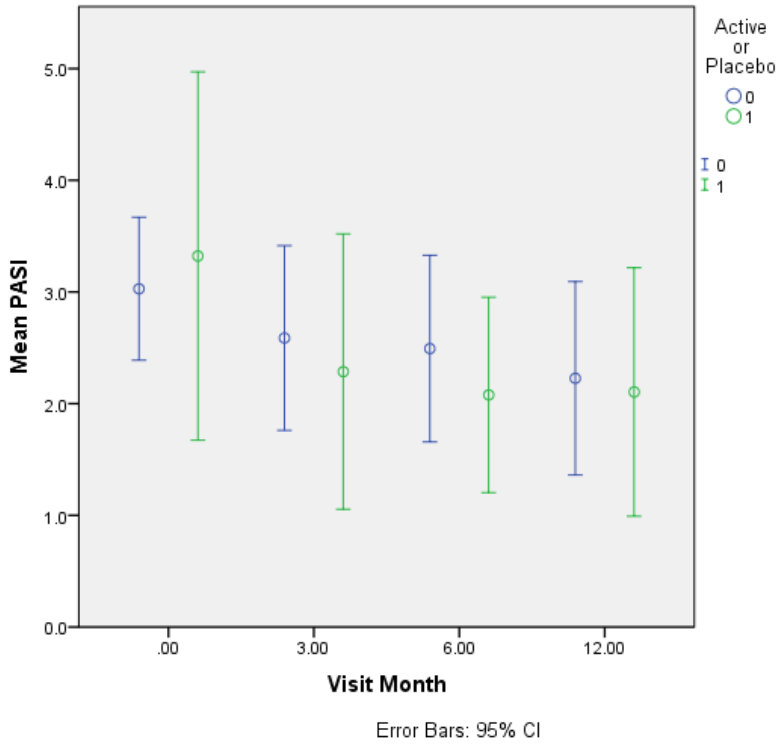
PASI = Psoriasis Area Severity Index, PGA = Physicians Global Assessment, DLQI = Dermatology Life Quality Index, PDI = Psoriasis Disability Index.

No adverse effects were reported in either the treatment or placebo groups.

6.3.4 Comparison of Outcome in the Placebo and Vitamin D_3 Groups by Mixed Model Methods

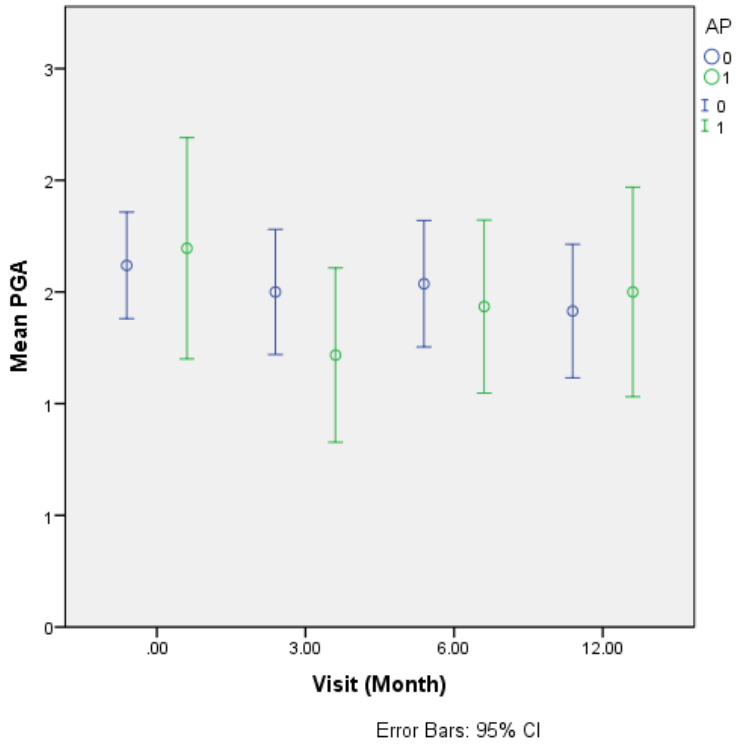
The means of the PASI, PGA, PDI and DLQI with 95% confidence intervals at baseline and follow-up visits are shown graphically in Figures 12, 13, 14 and 15.

Figure 12: Mean Psoriasis Area and Severity Index (PASI) score at each visit



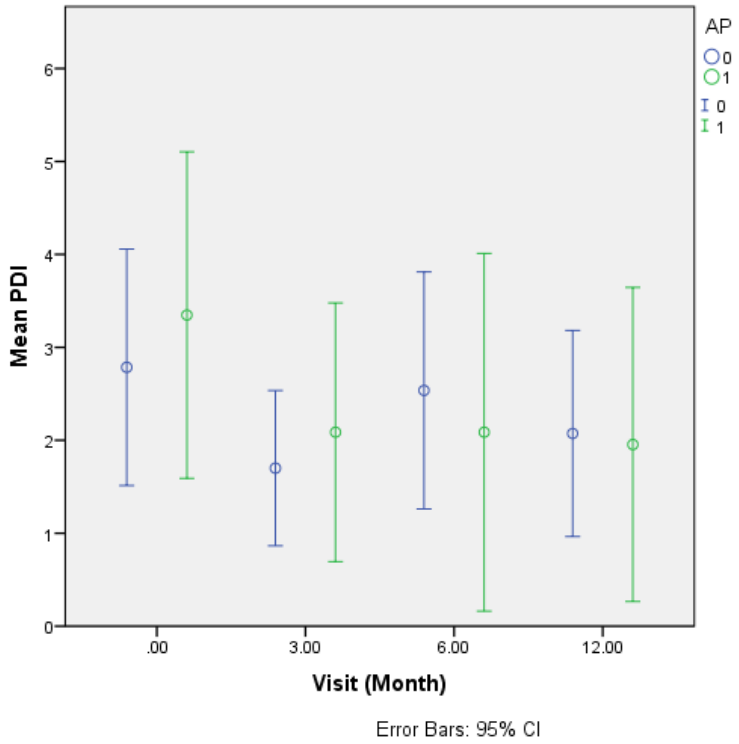
AP = Active/Placebo, 1 = Vitamin D group, 0 = Placebo.

Figure 13: Mean Physician Global Assessment (PGA) score at each visit



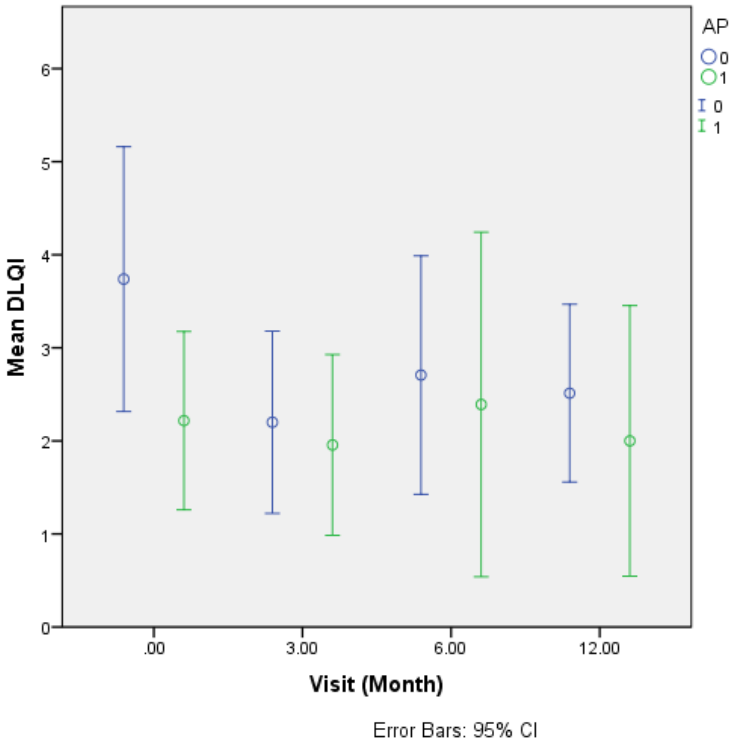
AP = Active/Placebo, 1 = Vitamin D group, 0 = Placebo.

Figure 14: Mean Psoriasis Disability Index (PDI) score at each visit



AP = Active/Placebo, 1 = Vitamin D group, 0 = Placebo.

Figure 15: Mean Dermatology Life Quality Index (DLQI) score at each visit



AP = Active/Placebo, 1 = Vitamin D group, 0 = Placebo.

The linear mixed model method was used to analyse the data over time of the four main dependent variables of PASI, PGA, DLQI and PDI. AR (1) covariance structure was selected and the results adjusted for change of treatment which was added as a covariate to the model. Tests for an interaction of active placebo*visit were not significant in any measured variable. The results, with p values in the footnote, are summarised in Tables 37, 38, 39 and 40.

Table 37: Linear mixed model analysis of Psoriasis Area and Severity Index (PASI) scores

	Estimated marginal mean PASI score (95% CI)			
Visit (month)	**0**	**3**	**6**	**12**
Placebo	3.0 (2.2,3.8)	2.5 (1.7,3.3)	2.5 (1.7,3.3)	2.2 (1.4,3.0)
Vitamin D	3.3 (2.2,4.4)	2.3 (1.2,3.4)	2.1 (1.0,3.2)	2.1 (1,3.2)

PASI = Psoriasis Area and Severity Index. CI = Confidence interval. p = 0.71 adjusted for covariate change of treatment.

Table 38: Linear mixed model analysis of Physicians Global Assessment (PGA) scores

	Estimated marginal mean PGA score (95% CI)			
Visit (month)	**0**	**3**	**6**	**12**
Placebo	1.6 (1.4,1.9)	1.5 (1.2,1.8)	1.5 (1.3,1.8)	1.4 (1.1,1.7)
Vitamin D	1.7 (1.3,2.1)	1.2 (0.8,1.6)	1.4 (1.1,1.8)	1.5 (1.1,1.9)

PGA = Physicians Global Assessment. CI = Confidence interval. p = 0.26 adjusted for covariate change of treatment.

Table 39: Linear mixed model analysis of Psoriasis Disability Index (PDI) scores

	Estimated marginal mean PDI score (95% CI)			
Visit (month)	**0**	**3**	**6**	**12**
Placebo	2.8 (1.6,3.9)	1.7 (0.6,2.9)	2.6 (1.4,3.7)	2.1 (0.9,3.2)
Vitamin D	3.3 (1.8,4.9)	2.1 (0.6,3.6)	2.1 (0.5,3.6)	1.9 (0.4,3.4)

PDI = Psoriasis Disability Index. CI = Confidence interval. p = 0.72, adjusted for covariate change of treatment.

Table 40: Linear mixed model analysis of Dermatology Life Quality Index (DLQI) scores

	Estimated marginal mean DLQI score (95% CI)			
Visit (month)	**0**	**3**	**6**	**12**
Placebo	3.7 (2.7,4.8)	2.2 (1.2,3.3)	2.8 (1.6,3.8)	2.5 (1.4,3.6)
Vitamin D	2.2 (0.8,3.6)	2.0 (0.5,3.4)	2.4 (1.0,3.8)	2.0 (0.5,3.4)

DLQI = Dermatology Life Quality Index. CI = Confidence interval. p = 0.47, adjusted for covariate change of treatment.

6.4 Discussion

This placebo-controlled, double-blind study of the addition of 100,000 IU vitamin D_3 (cholecalciferol) each month over 12 months, in patients who have mild psoriasis, did not demonstrate a therapeutic effect as measured by the PASI or PGA. Furthermore, there was no change in the quality of life by the addition of vitamin D_3, measured by the DLQI and PDI. Therefore vitamin D_3 supplementation cannot be recommended as an effective therapy for mild psoriasis.

The psoriasis study recruited 65 participants from the ViDA pool of 5,110 participants which represents 1.3% of the group. Therefore, this is likely to be a true representation of the prevalence of psoriasis from within this group as, within the population as a whole, psoriasis prevalence is estimated to be between 1 and 2% (134). Psoriasis, as rated by the physician rather than the patient, is often rated as mild in the community setting. In a population-based cross-sectional study of 9,035 patients, which assessed psoriasis by BSA (where mild was defined as ≤ 2% BSA and severe as ≥ 10% BSA), 51.8% were assessed as mild and 12.4% as severe (318). Therefore the psoriasis participants from the ViDA study are likely to be representative of the population.

The severity of the participant's psoriasis was not a criteria for entry into the study and only those who fell within the overall criteria for entry into the large ViDA study could participate in the psoriasis substudy, so younger participants aged < 50 were excluded and perhaps selecting patients only with moderate to severe psoriasis may have shown a treatment effect of vitamin D_3. The PASI and PGA are clinical measures of psoriasis and may not be sensitive enough to document small change, however in the clinic, a clinically meaningful change needs to be demonstrated for an intervention to be useful and this was not the outcome from this study.

For financial reasons, it was not possible to measure the 25-hydroxyvitamin D of the participants as they were observed during the 12-month trial. Therefore, it is not possible to confirm that the 25-hydroxyvitamin

D did rise into the intended range of > 80 nmol/l. However, the compliance checks did not suggest that the vitamin D or placebo was not being taken.

The unbalanced numbers between the placebo and vitamin D groups was surprising in light of the randomisation process and there is no clear explanation for the approximate 2:1 ratio of placebo to vitamin D participants which was most likely due to chance. Despite this uneven ratio, the two groups were very well matched.

The implications of these results are further discussed in Chapter 8.

6.5 Summary

Chapter 6 is the description of a placebo-controlled study of the use of vitamin D_3 in the management of mild psoriasis with patients who were recruited from a larger study. There was found to be no clinical effect of supplementation on the activity of mild psoriasis, as measured by the PASI and PGA, or the quality of life, as measured by DLQI or the PDI.

Chapter 7 Psoriasis and Cardiovascular Risk

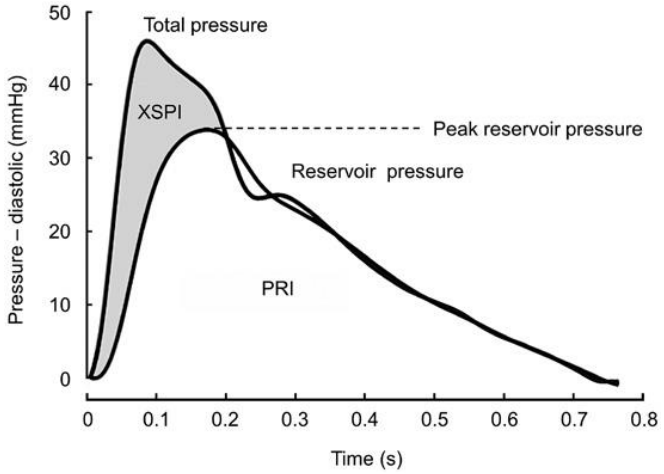
7.1 Introduction

This chapter describes the method, results and conclusions of a substudy to assess aspects of cardiovascular risk of the psoriasis participants compared with the other participants in the ViDA study who did not have psoriasis.

The literature review (see Chapter 4, Section 4.5) has discussed the association of moderate and severe psoriasis with cardiovascular disease and particularly the risk of atherosclerosis as these diseases share common inflammatory pathways. The ViDA study recorded several measurements of cardiovascular risk at the baseline interview including cardiovascular risk factors as reported by the participant and measured a number of physiological variables related to cardiovascular risk including weight, total cholesterol, HDL cholesterol, blood pressure and the excess pressure integral (EPI).

The EPI is a measure of the additional or unnecessary work done by the left ventricle and is an independent risk factor for cardiovascular disease (319). The EPI is derived from an analysis of the arterial waveform, which was measured by the Pulsecor device (320, 321). As the heart pumps, a waveform is generated that travels through the arterial system both forward from the heart and then backward by reflection from distal locations. In the presence of diseased (sclerotic and stiff) vessels the waveform will be different from that of healthy vessels. The EPI is the difference between the measured blood pressure waveform and the integral of reservoir pressure which is a measure of the theoretical minimum hydraulic work needed to generate the required stroke volume in each cardiac cycle. A higher EPI indicates circulatory dysfunction. An example of the separation of the measured waveform into EPI and reservoir pressure is shown in Figure 16 taken from Davies et al (319).

Figure 16: The separation of the measured waveform into excess pressure integral and reservoir pressure taken from *Davies et al, 2014* (319)



A further measure derived from waveform analysis is the augmentation index (AIx) which is a measure of the arterial stiffness. It can be calculated from the pressure waveform measured by the Pulsecor device and is calculated by augmentation pressure as a percentage of aortic pulse pressure, where the former is the

difference between the second and first systolic peaks (322). Arterial stiffness is associated with increased cardiovascular risk (323, 324) and an elevated AIx is associated with increased cardiovascular risk (325).

A study by Balta et al (326) examined 32 patients with psoriasis and compared them with 35 patients with other skin diseases. Pulse wave velocity (PWV) was measured as a marker of arterial stiffness. The absolute PASI values were not recorded but there was no correlation between PASI score and PWV. However, in another study by Sunbul et al (327), 50 patients with psoriasis were compared with 50 controls and the AIx and PWV were found to be significantly higher in the psoriatic patients ($p = 0.001$ and $p = 0.011$ respectively).

7.1.1 Aim

The primary aim of this study was to determine if the participants in the ViDA study with psoriasis had significantly different cardiovascular risk factors to the control group. The secondary aim was to examine if the arterial waveforms differed between the groups, and if there was a relationship between the waveform and the severity of psoriasis as measured by the PASI.

7.2 Method

All participants in the ViDA study completed a baseline questionnaire. The ViDA baseline questionnaire is a comprehensive investigation of the participant demographics, lifestyle, general health, past medical history and medication history. At the ViDA baseline interview a number of physiological variables were also measured including the EPI and AIx calculated from variables measured by the Pulsecor device.

Baseline data were extracted from the ViDA database and placed in an Excel spreadsheet. The data extracted were demographic details and specific cardiovascular risk factors relating to aspects of cardiovascular disease. The data examined in relation to cardiovascular history were diabetes, smoking, hypertension and physical activity. These risk factors were identified by the participant answering the questions:

- *"Have you ever been told by a doctor that you have diabetes?"*
- *"Have you ever smoked cigarettes or tobacco at all, even just a few puffs? Please include pipes, cigars and tobacco products only."*
- *"Have you ever been told by a doctor that you have high blood pressure?"*

Physical activity was identified by the response to the question:

- "*In a typical week during the last three months did you practise any of these activities vigorously enough to cause sweating or faster heartbeat?"*

This question was posed following the reply to the preceding question which was, *"In a typical week during the last 3 months, how many hours did you spend on each of the following activities?"* and was asked only if the participant spent at least 1 hour undertaking the activities which were walking, cycling, gardening, housework, do it yourself, other physical activities such as keep fit, aerobics, swimming and jogging.

The physiological data used included weight, blood pressure, total cholesterol, HDL cholesterol and EPI. BMI was calculated from the weight (wt) and height (ht) by the equation ($BMI = wt/[ht]^2$).

Patients who were identified as having psoriasis were compared with the control group. The control group were all the other participants in the ViDA study. Statistical analysis was undertaken using SPSS version 22.

7.3 Results

7.3.1 Baseline Comparison of Control and Psoriatic Groups

The control and psoriatic groups were compared and found to be well matched. The baseline demographic data of the control and psoriasis groups are summarised in Table 41.

Table 41: Comparison of the psoriasis and control group—demographic details and categorical risk factors for cardiovascular disease

	Psoriasis		
	Yes	**No**	**p value**
Number (%)	65 (1.3)	5,045 (98.7)	
Sex (%)			
Male	39 (60)	2,923 (58)	
Female	26 (40)	2,111 (42)	
Total	65	5,034	
Missing	0	11	0.75
Age group years (%)			
50–59	12 (18.5)	1,132 (22)	
60–69	36 (55)	2,195 (44)	
70–79	14 (21.5)	1,398 (28)	
80–84	3 (5)	306 (6)	
Total	65	5,031	
Missing	0	14	0.30
Ethnicity (%)			
European	60 (92)	4,195 (83)	
Māori	2 (3)	270 (5)	
Pacific	2 (3)	332 (7)	
Asian	1 (1)[A]	248 (5)	
Total	65	5,045	0.40*
Smoking (%)			
Yes	52 (80)	3,559 (71)	
No	13 (20)	1,471 (29)	
Total	65	5,030	
Missing	0	15	0.10
Diabetes (%)			
Yes	7 (11)	615 (12)	
No	58 (89)	4,414 (88)	
Total	65	5,029	
Missing	0	16	0.72
Hypertension (%)			
Yes	23 (65)	2,180 (56)	
No	42 (35)	2,828 (43)	
Total	65	5,008	
Missing	0	37	0.19
Physical activity (%)			
Yes	43 (66)	2,924 (59)	
No	22 (34)	2,009 (41)	
Total	65	4,933	
Missing	0	112	0.26

* Fisher's exact.

A chi-square test of independence was performed to examine differences between the control group and the psoriatic group for both age and ethnic distribution. There was no significant difference between the two groups (χ^2) for age or ethnicity at p = 0.43 and p = 0.26 respectively.

The mean (SD) PASI of the participants who had psoriasis was 3.1 (± 2.8).

7.3.2 Comparison of Cardiovascular Risk Factors of Control and Psoriatic Groups

Independent *t* tests were performed to examine the association of cardiovascular risk factors in the control and psoriatic groups. These are summarised in Table 42.

Table 42: Univariate analysis of mean (SD) cardiovascular risk factors between psoriasis group and controls

	Psoriasis		
Risk factor	**Yes**	**No**	**p value***
Blood pressure Systolic Diastolic	 137 (± 18) 77 (± 11)	 139 (± 19) 78 (± 10)	 0.42 0.26
Total cholesterol (mmol/l)	4.8 (± 1.2)	4.8 (± 1.1)	0.97
HDL (mmol/l)	1.3 (± 0.3)	1.4 (± 0.4)	0.05**
BMI (kg/m^2)	28.8 (± 4.9)	28.4 (± 5.1)	0.54
Excess pressure integral (mmHg/s)	4.06 (± 2.59)	3.91 (± 1.8)	0.51
Augmentation index	29.3 (± 12.5)	28.6 (± 12.2)	0.64

SD = Standard deviation. *t test, HDL = High density lipoprotein, BMI = Body mass index independent. **Levene's test is significant (p = 0.034) therefore equal variances not assumed (HDL Kolmogorov-Smirnov test p < 0.001).

A linear regression analysis of all of the participants was undertaken for the EPI and AIx. The diagnosis of psoriasis was not found to be a significant factor in either. This is summarised in Table 43.

Table 43: Multiple linear regression for excess pressure integral and augmentation index as outcome variables

	Excess pressure integral (mmHg/s)		Augmentation index (%)	
Variable	**Coefficient estimate (95% CI)**	**p value**	**Coefficient estimate (95% CI)**	**p value**
Constant	−0.004 (−0.6,0.6)	0.988	−8.5 (−12.9,−4.1)	0.000
Age	0.002 (0.0,0.01)	0.411	0.09 (0.05,0.13)	0.000
Diastolic blood pressure	−0.10 (−0.1,−0.1)	0.000	−0.04 (−0.08,0.00)	0.037
Systolic blood pressure	0.8 (0.08,0.09)	0.000	0.3 (0.2,0.3)	0.000
Total cholesterol	−0.05 (−0.1,−0.01)	0.020	−0.3 (−0.6,0.0)	0.053
HDL cholesterol	0.07 (−0.04,0.20)	0.192	5.2 (4.3,6.0)	0.000
BMI	0.02 (0.01,0.02)	0.000	−0.30 (−0.3,−0.2)	0.000
Diabetes (Yes/No)	−0.05 (−0.2,0.06)	0.354	−2.1 (−2.9,−1.2)	0.000
Physical activity (Yes/No)	−0.01 (−0.06,0.04)	0.628	−0.5 (−0.9,−0.1)	0.014
Smoker (Yes/No)	−0.52 (−0.1,0.03)	0.211	−0.5 (−1.2,0.1)	0.103
Psoriasis (Yes/No)	0.20 (−0.2,0.5)	0.369	1.6 (−1.0,4.3)	0.229

CI = Confidence interval, BMI = Body mass index, HDL = High density lipoprotein.

7.3.3 Analysis of Psoriatic Group Excess Pressure Integral and Augmentation Index

The psoriatic group alone was analysed for cardiovascular risk dependent on PASI. To assess if the severity of psoriasis, as measured by the PASI, was a determinant of the waveform correlation, multivariate analysis was undertaken.

There was no correlation between the PASI and the EPI or the AIx. The results are summarised in Table 44.

Table 44: Correlation coefficient PASI with excess pressure integral and augmentation index

	PASI	
	Spearman rho*	**p**
EPI	0.12	0.36
AIx	0.16	0.20

PASI = Psoriasis Area and Severity Index, EPI = Excess pressure integral, AIx = Augmentation index. * Distribution not normal therefore spearman rho calculated.

Multiple linear regression with EPI and AIx as the dependent variables was undertaken and dummy variables were created for psoriasis (yes = 1, no = 0), diabetes (yes = 1, no = 0), smoking (yes = 1, no = 0), and physical activity (yes = 1, no = 0), also controlling for age as a continuous variable, systolic and diastolic blood pressure, total and HDL cholesterol and BMI to adjust for the variables in the psoriasis group. The distribution of the EPI was not normal (Kolmogorov-Smirnov test $p < 0.001$) and therefore was log transformed. PASI was found not to be a significant factor for either outcome variable. The results are summarised in Table 45.

Table 45: Multiple linear regression of the psoriatic group only with excess pressure integral and augmentation index as the outcome variables

	Excess pressure integral (mmHg/s)		Augmentation index (%)	
Variable	**Coefficient estimate (95% CI)**	**p value**	**Coefficient estimate (95% CI)**	**p value**
Constant	0.67 (−0.50,1.83)	0.25	−23.9 (−59.8,12.0)	0.19
PASI	0.01 (−0.02,0.05)	0.33	0.23 (−0.7,1.2)	0.6
Gender	0.04 (−0.1,0.2)	0.66	13.1 (7.2,18.8)	<0.001
Age	0.01 (−0.01,0.02)	0.32	0.29 (−0.06,0.6)	0.10
Diastolic blood pressure	−0.02 (−0.03,−0.01)	<0.001	0.18 (−0.15,0.5)	0.27
Systolic blood pressure	0.02 (0.01,0.02)	<0.001	0.19 (0.0,0.4)	0.05
Total cholesterol (mmol/l)	−0.08 (−0.16,0.003)	0.06	−1.79 (−4.40,0.81)	0.17
HDL cholesterol (mmol/l)	0.19 (−0.1,0.5)	0.22	4.84 (−4.9,14.5)	0.32
Smoker	−0.11 (−0.3,0.1)	0.30	0.4 (−6.0,6.9)	0.90
Diabetes	0.09 (−0.2,0.4)	0.53	0.7 (−7.9,9.3)	0.90
Hypertension	−0.12 (−0.2,0.2)	0.90	–2.2 (−7.8,3.4)	0.43
Physical activity	0.04 (−0.1,0.2)	0.66	−1.9 (−7.5,3.7)	0.50
BMI	−0.01 (−0.03,0.01)	0.30	−0.3 (−1.0,0.3)	0.33

PASI = Psoriasis Area Severity Index, HDL = High density lipoprotein, BMI = Body mass index, CI = Confidence interval.

7.4 Discussion

The substudy has shown that the participants in the ViDA study with psoriasis are not at greater risk of cardiovascular disease compared with the other participants in the study when their risk factors are assessed. There was no significant difference in the lifestyle markers of the two groups including diabetes, smoking, hypertension and physical activity based on the self-reported information collected at baseline. There was also no significant difference in the measured physiological variables of blood pressure (systolic and diastolic), cholesterol (total), or BMI when assessed by independent *t* tests.

The secondary aim of the study was to see if a significant difference existed between the EPI and the AIx of the psoriatic participants compared with controls. Multiple linear regression analyses were undertaken using EPI and AIx as the dependent variables and controlling for age, blood pressure (systolic and diastolic), total and HDL cholesterol, BMI, diabetes, physical activity, smoking and psoriasis. Significant factors associated with the EPI and AIx were blood pressure (both systolic and diastolic), total cholesterol and BMI. Diabetes and physical activity were significant for the augmentation index only. For both EPI and AIx, the diagnosis of psoriasis was not associated, not supporting the findings of Sunbul et al (327).

The participants of the ViDA psoriasis substudy had mild psoriasis with a mean PASI of 3.1. The use or need for systemic therapy can be used as a proxy for severity of psoriasis. The definition of severe psoriasis as scored by the PASI varies but in the UK the National Institute for Health and Care Excellence (NICE) advise systemic therapy for psoriasis when the PASI is greater than 10 and in New Zealand the PHARMAC criteria for eligibility for biologic therapy is a PASI greater than 15. As discussed in the literature review, the greatest risk in terms of cardiovascular disease for those who have psoriasis are those with severe disease usually graded as a PASI greater than 10. It is therefore reassuring, for those with mild psoriasis, that this study adds to evidence that the cardiovascular risk is not increased in these patients.

The psoriatic group was analysed separately. PASI was not associated with EPI or AIx in unadjusted analyses nor in multivariate analyses adjusted for gender, age, blood pressure (diastolic and systolic), cholesterol (total and HDL), BMI, smoking, diabetes, hypertension and physical activity. The study by Boehncke et al examined 37 patients with moderate to severe psoriasis, however the average PASI score was not recorded. There was no correlation between vessel wall thickness, measured by ultrasound, and PASI ($p = 0.80$). Furthermore, Boehncke's study found no correlation between BMI and PASI ($p = 0.957$) and this finding concurs with the ViDA substudy finding, $r_s(65) = .03$ $p = 0.811$ (275).

There was no association between physical activity and PASI scores within the psoriatic group or comparing the psoriatic group physical activity with controls. The low PASI scores in the group may again be significant in the understanding of this analysis, as any exercise may have only a small effect if any, when the psoriasis is mild.

The selection of the psoriatic group may not reflect the general population as a whole as all the members were derived from a subgroup of the ViDA recruited population needing to meet the ViDA requirements for entry into the study.

The implications of these results are further discussed in Chapter 8.

7.5 Summary

There is no significant increase in cardiovascular risk in the ViDA psoriasis patients compared with controls and this supports the view that mild psoriasis does not carry an increased risk of cardiovascular disease.

Chapter 8 Thesis Discussion

8.1 Introduction

Chapter 8 focuses on each of the four studies of the thesis placing them in the context of current knowledge, discussing the implications of the thesis data and specifically, given the findings of the literature review, why 25-hydroxyvitamin D was not found to be relevant to cutaneous lupus and did not have a clinically meaningful effect on psoriasis. It also summarises the general strengths and weaknesses of the studies. Finally, the implications for future research are discussed.

The work of the thesis has involved three different study designs to address specific gaps in knowledge. The first was a retrospective study of cutaneous lupus to assess prevalence within a geographically defined area (CMDHB) which contained a widely diverse population. The second study, using data generated from the first study, was a cross-sectional study examining the role of 25-hydroxyvitamin D status in cutaneous lupus, again drawing on the CMDHB population. The third study was a prospective, randomised, placebo-controlled trial examining the effect of vitamin D_3 supplementation on patients with psoriasis. The sample population was not confined to Counties Manukau but encompassed the wider Auckland population. The third study also allowed an examination of the cardiovascular risk factors in the group of patients who had psoriasis within the ViDA population and specifically examined this risk in relation to arterial waveform measures.

The author of this thesis was responsible for the design and full undertaking of the first two studies. For the third study, the author advised on the outcome psoriasis measures and undertook all the clinical assessments required. The baseline waveform data were taken by the ViDA staff. The structure of the ViDA study was established prior to the initiation of the psoriasis substudy.

8.2 Prevalence of Cutaneous Lupus

This is the first study to assess the prevalence of cutaneous lupus in a New Zealand population and to examine the prevalence by ethnicity. The study was a population-based assessment intentionally examining multiple databases from both the hospital and community in an attempt to identify every patient with cutaneous lupus. The study showed for the first time that Māori and Pacific have a higher relative risk of 2.47 (95% CI: 1.67–3.67) for cutaneous lupus compared with the European population in South Auckland, when adjusted for age and sex. DLE in Māori and Pacific carries a higher relative risk compared with the European population of 5.96 (95% CI: 3.06–11.6) when adjusted for age and sex. In all types of cutaneous lupus, the relative risk is higher for females than males at 1.66 (95% CI 1.55–1.78).

The prevalence study found a total of 145 patients with confirmed cutaneous lupus. These absolute numbers make this one of the larger studies of the prevalence of cutaneous lupus, only exceeded by Durosaro et al (108) with a total of 156 patients. Durosarao et al comment that their figures may be an underestimate of the true prevalence as their population was predominately white and not ethnically diverse. In the 2005 US census the population distribution of Olmsted County, the population investigated,

was 89.9% white and 3.6% African-American (108). A summary of the prevalence of cutaneous lupus per 100,000 of the population in the three studies that examine cutaneous lupus and give prevalence rates is given in Table 46.

Table 46: Summary of prevalence studies of cutaneous lupus (per 100,000 of population)

Author	Ethnicity	All types of cutaneous lupus (95%CI)	ACLE	SCLE	DLE
Popovic (107)	European	NG	NG	6.2–14	NG
Durosaro (108)	NG	73.24 (58.29–88.19)	NG	NG	NG
Jarrett	Māori/Pacific	42.2 (33.87–52.59)	12.82 (8.62–19.08)	0.53 (0.09–3.02)	27.24 (20.73–35.82)
	Indian/Asian	22.55 (14.44–35.23)		2.37 (0.65–8.66)	
	European	25.75 (19.36–43.23)		8.77 (5.40–14.24)	

ACLE = Acute cutaneous lupus, SCLE = Subacute cutaneous lupus, DLE = Discoid lupus, NG = Not given.

Durosaro's study, which was also a community-based project, shows prevalence figures which are higher than those of this study. The ethnicity of the Rochester, Minnesota, USA patients was not recorded in this study. The study of Popovic from Stockholm County, Sweden does give similar figures for the prevalence of SCLE for the European population of CMDHB. Although the ethnicity of the Swedish study was not recorded, a personal communication with Professor Nyberg, a co-author of the paper, confirmed it was mainly Caucasian.

Why do Māori and Pacific in New Zealand have a higher prevalence of cutaneous lupus and especially DLE? Firstly, however, should all three types of cutaneous lupus—ACLE, SCLE and DLE—be considered as different subgroups of the same disease? This is an accepted dogma which was recently confirmed in the European classification (101). Morphologically and serologically this can be argued for ACLE and SCLE which show clinical overlap. A proportion of SCLE and DLE patients develop SLE (108), but should DLE be considered under the same umbrella? The clinical features and behaviour of DLE are different to the other two subtypes and the serology is dissimilar as well. This study has shown that many patients with DLE are ANA negative, unlike ACLE or SCLE, a finding also described by Ng et al (328). The three types share some common histological features but so can psoriasis and eczema which are dogmatically regarded as different diseases. The fact that this study also found such a marked difference in DLE relative risk in Māori and Pacific points to DLE behaving differently at least in those ethnic groups, compared with the European group. There was also a trend, although not significant, that SCLE was more common in the European group compared with Māori and Pacific, suggesting that this disorder also behaves differently between the two groups.

So it is uncertain why Māori and Pacific together have a higher prevalence of cutaneous lupus compared with other groups or why DLE is particularly prevalent. Perhaps there are common genetic factors given the shared common ancestry described in Chapter 2. The genetics of DLE have not been examined in Māori and Pacific people, although some genetic studies in other populations do exist. Ten patients in Scandinavia with DLE, who had lesional biopsies, were found to have 13 translational hot spots (329). In a

Finnish study, polymorphisms of the ITGAM gene (a member of the immune complex processing pathway) confer a threefold increased risk of DLE compared with healthy individuals, and the magnitude of the association is five times higher in DLE than in SLE patients (330). Furthermore, human leukocyte antigen associations in DLE have been described in European and Mexican populations (331, 332). Genetic studies of Māori and Pacific patients with DLE are needed.

Chapter 4, Section 4.1.1 reviewed not only cutaneous lupus but also systemic lupus, finding that non-white groups have a higher prevalence of systemic lupus compared with white groups, and this has been noted for Māori/Pacific in Auckland, New Zealand (106) and the Polynesian population of Hawaii (105) as well. So could skin colour itself be a risk factor for developing cutaneous lupus, given that Auckland Māori/Pacific have a higher relative risk compared with the European population? There are no studies of cutaneous lupus in countries where patients have not migrated from their evolutionary ancestry. For example, it would be interesting to know the prevalence of cutaneous lupus in Addis Abba, Ethiopia at latitude 9.03° N now that the prevalence is known in Minnesota, USA at 44° N and Auckland, New Zealand at 38.8° S. However, this thesis did not demonstrate a higher prevalence of cutaneous lupus in the Auckland Indian and Asian populations, also groups with coloured skin, which suggests that genetics are more important than skin colour.

At a local level, and taking a wider view beyond cutaneous lupus, many diseases are unfortunately more common in Māori and Pacific in CMDHB compared with other population groups, including diabetes, coronary heart disease, cerebrovascular disease, hypertension, gout, cancer, asthma, and serious mental illness (333). The association of disease with poverty is well recognised. Nearly three-quarters of Pacific and more than half of the Māori population in CMDHB live in high deprivation areas compared with other ethnic groups (333). Thus, socioeconomic and lifestyle factors may also contribute to the ethnic variations in risk.

The thesis study of the prevalence of cutaneous lupus has some weaknesses and strengths. The study is a retrospective look at notes and relies on adequate detail to establish a diagnosis of cutaneous lupus. The diagnosis that is particularly vulnerable is that of ACLE and to a lesser extent SCLE. ACLE is often an evanescent rash and at the time of presentation of systemic lupus may not be the primary treatment focus when, for example, significant arthritis, renal or haematological disease is present. Effective treatment for these problems will promptly resolve the usually non-scarring rash. Additionally, the presence of the rash often relies on non-dermatologists for identification. Furthermore, the diagnostic criteria for systemic lupus, including a malar or discoid rash (99), and lack of dermatological precision may lead to over-diagnosis of cutaneous lupus among non-dermatologists and the rash of cutaneous lupus may predate or postdate the diagnosis of systemic lupus, further confounding the ability to accurately assess the true prevalence. For this study, care was taken to select only cases where there was clear recording of the rash of ACLE and as such may underestimate the true population. SCLE is less vulnerable as it is usually not associated with systemic symptoms but may be evanescent. The data on DLE are more robust as it is a chronic problem and when established does not resolve quickly and easily. It is a distinctive and unusual rash which would prompt referral. Scarring generates patient concern and therefore additional pressure to refer to a dermatological service. Scarring is a permanent record of the disease. It was not possible in this study to meaningfully interpret the rarer examples of cutaneous lupus (chilblain, panniculitic and tumid).

Occasionally, it is not possible to clinically accurately describe cutaneous lupus into any category when a mixture of clinical signs is present; however, this study did not identify any such cases.

In an attempt to ascertain every case in the CMDHB community, many data sources were examined and multiple health care professionals, including those in the private sector who care for such patients were approached. It is acknowledged, however, that some cases will not have been identified and this was mitigated to a degree by the capture-recapture estimate analysis.

8.3 Cutaneous Lupus and Vitamin D Status

The second thesis study examined 25-hydroxyvitamin D levels and cutaneous lupus and did not find an association. This study, of 80 patients, is the largest study to date of 25-hydroxyvitamin D and cutaneous lupus. It recruited the required number of patients (n = 80) to satisfy the power calculation to detect a difference of 3.2 nmol/l between the case and control groups. It is also the only study to assess, in depth, the activity and damage caused by cutaneous lupus with 25-hydroxyvitamin D levels using the CLASI scoring system. The finding of no significant association is consistent with the findings of Word et al (118) mentioned briefly in their study of African-Americans, Caucasian and Hispanic Americans (see Chapter 4, Section 4.1.2.1).

Why did the study not find 25-hydroxyvitamin D deficiency in the patients with cutaneous lupus? Perhaps it does not exist. A problem is that of the definition of deficiency. The thesis study used the New Zealand Ministry of Health definition (see Chapter 3, Section 3.1.3) and deficiency is discussed in Section 3.1.3. The studies of 25-hydroxyvitamin D and cutaneous lupus are discussed in Chapter 4, Section 4.1.2.1. The published studies have varying definitions of deficiency/insufficiency. For example, Cusack et al (114) did not report their definitions of deficiency but noted “a desirable vitamin D level of 75 nmol/l”; Renne et al (115) reported it was “widely accepted to define levels of < 50 nmol/l (20 ng/ml) as deficient”, as does the paper by Heine et al (116). Cutillas-Marco et al (117) use < 75 nmol/l as the “accepted lower limit for vitamin D adequacy” and Word et al (118) reported “vitamin D insufficiency (defined as < 50 nmol/l)”. The broad view of SLE, as opposed to cutaneous lupus only, is that most show an association with low 25-hydroxyvitamin D levels (see Chapter 4, Section 4.1.3).

Regardless of definitions, all the 25-hydroxyvitamin D means, in all ethnicities in the cases in this thesis, were > 50 nmol/l—equal to or above the recommended levels as defined by the New Zealand Ministry of Health definition. The second study also confirmed that Māori and Pacific have greater odds of cutaneous lupus, despite passive selection bias, compared with the European population, with an odds ratio of 9.6 (95% CI: 5.6, 16.4). It is uncertain why fewer Māori and Pacific (n = 30) were recruited to this study compared with the European recruitment (n = 43). The recruitment strategy was the same for all ethnicities and an alternative approach to Māori and Pacific may have yielded great numbers. Culturally appropriate approaches could include involving key community members and full translation of the patient information leaflet into Te Reo Māori and Pacific languages (334). However, the fiscal limits of the study would not permit this approach.

There was no significant difference between 25-hydroxyvitamin D levels of European, Pacific and Māori cases and controls ($p > 0.05$) within the thesis study, which argues strongly that 25-hydroxyvitamin D is not

a significant factor in cutaneous lupus. Furthermore, an examination of the mean 25-hydroxyvitamin D levels between the studies around the world which report them, show that despite higher levels of 25-hydroxyvitamin D reported in this thesis compared with those in Europe and the USA, cutaneous lupus remains prevalent in Auckland, New Zealand (Table 47). The combined mean (SD) 25-hydroxyvitamin D level for Māori/Pacific, an at-risk group for cutaneous lupus, was 75.1 (± 29.8) nmol/l which is higher than all of the other means.

Table 47: Summary of the mean 25-hydroxyvitamin D levels of patients with cutaneous lupus from the studies where the data are available

Study	Location	Study recruitment period	Latitude	Mean 25-hydroxyvitamin D of all lupus cases nmol/l (SD)
Cusack (114)	Dublin, Ireland	July–September 2006	53.35° N	63.0 (±23.3)
Cutillas-Marco (117)	Valencia, Spain	May–October 2008	39.47° N	49.9 (±22.2)
Word (118)	Dallas, USA	April 2007–March 2011	32.78° N	52.0 (±18.5)
Jarrett	Auckland, NZ	January–May 2011	36.84° S	88.6 (±33.6)

SD = Standard deviation.

Therefore, despite the differing environments between Europe, USA and New Zealand, and two of the three published studies also including the northern hemisphere summer period (114, 117), no study found a mean below 50 nmol/l and therefore 25-hydroxyvitamin D deficiency (defined as a level < 50 nmol/l) appears not to be an important factor overall in cutaneous lupus.

The thesis study population was skewed towards low CLASI activity and low CLASI damage (see Chapter 5, Section 5.3.4.4) which does raise the possibility of a type 2 error due to too few patients with severe disease. An exploration of the data limiting the examination of CLASI activity and damage to be > 10 did not find an association with 25-hydroxyvitamin D levels. Therefore, to examine this possibility further, larger numbers of patients with significant lupus activity and damage would be needed and to achieve this goal, a multisite study would be required. However, individually, patients remain at risk of deficiency of 25-hydroxyvitamin D because of the need for sun protection to prevent cutaneous lupus exacerbation but, if deficiency is found, it seems not to be a driver of the activity or damage associated with cutaneous lupus, based on the thesis results.

The arguments about the classification of cutaneous lupus discussed in Section 8.2 could equally apply to this section of the discussion because, for the purposes of the analysis of this study, the differing types of cutaneous lupus were regarded as variants of the same disease.

8.4 Psoriasis and Vitamin D

The randomised, placebo-controlled study of the supplementation of vitamin D_3 100,000 IU per month showed no effect on the parameters measured, which were the PASI, PGA, DLQI or the PDI. Although the study design was strong in its ability to prove causation, the small sample size is a weakness. Psoriatic keratinocytes have 1, 25 dihydroxyvitamin D_3 receptors (Table 6) (141) and the topically applied vitamin D_3 analogue, calcipotriol, is an effective treatment (see Chapter 4, Section 4.2.4) (191). So why is oral supplementation with vitamin D_3 (cholecalciferol) ineffective?

Psoriasis is an extraordinarily complex disease and the debate around the homogeneity of cutaneous lupus as one single disease, or more than one, can be applied to psoriasis. For example, for many years pustular psoriasis was regarded as a variant of psoriasis. However, generalised pustular psoriasis without a previous history of psoriasis has a different genetic basis to generalised pustular psoriasis with a history of psoriasis, with the former being associated with recessive mutations of IL36RN, which is an interleukin-36 antagonist. Additionally, for those patients with generalised pustular psoriasis and psoriasis, CARD4 p.Asp.176His gain of function variant is a predisposing factor (335). There were no participants with pustular psoriasis in this study. There are also genetic differences in the interleukin-1B gene between late onset psoriasis (over 40 years of age) compared with early onset psoriasis (less than 40 years of age) (336). Perhaps, with time, psoriasis will be further split into different subtypes depending on yet to be found genetic or other predisposing factors. Therefore, disease heterogeneity may be an issue for a variable response to cholecalciferol. Variations in the VDR appear not to be important (148).

A type 2 error is also possible as sample size is an issue for this study. Theoretically, with 65 participants and a randomised process, the two groups should have been roughly equal rather than a two-thirds/one-third split between placebo and active group. The cause is uncertain but probably due to chance. Despite this disparity the baseline parameters were similar, supporting the adequacy of the randomisation process. The previous studies summarised in Chapter 4, Section 4.2.3 do not give an accurate guide as to likely treatment effect of oral supplementation as they mostly do not use the PASI and are all uncontrolled. Therefore, calculation of power for the study is problematic. Furthermore, the population of the psoriasis group could only be drawn from the ViDA participant population rather than the community population as a whole. Additionally, the mild psoriasis in ViDA may have compounded the problem of identifying a treatment effect. Perhaps a study with moderate or severe psoriasis, with a PASI greater than 10, may yield differing results as any change would be easier to discern. Typical endpoints for psoriasis trials would be a reduction of a PASI score by 75% (PASI 75). For example, a recently published placebo-controlled study of the use of secukinumab (an anti-interleukin-17A antibody) had a baseline mean PASI > 20 in the two active treatment arms and the placebo. This study achieved a PASI 75 of 81.6% and 71.6% at 12 weeks by dosing with 300 mg or 150 mg respectively, with 200 and 174 patients in each group (138).

The basic science discussed in Chapter 4, Section 4.2.1.1 does show an effect of oral cholecalciferol supplementation on IL-17 levels in those who are deficient (158) and a localised effect when applied topically as calcipotriol (161). This provides a rationale for vitamin D supplementation in psoriatic patients who are deficient in 25-hydroxyvitamin D. It is possible, based on the theoretical knowledge, and evidence from one case report (179) and the group of nine patients with psoriasis who were below the recommended 25-hydroxyvitamin D_3 levels in Finamor's study (188) (see Chapter 4, Section 4.2.3), that 25-hydroxyvitamin D_3 will provide an adjunctive effect with other treatments for psoriasis, in the same way that 25-hydroxyvitamin D_3 may modulate immune function in the management of tuberculosis (265, 337) and supplementation improved SCORAD in Samochocki's study of atopic eczema (204) (see Chapter 4, Section 4.3.1).

Perhaps the localised effect of topical calcipotriol and the lack of effect of oral cholecalciferol in the ViDA study relates to the dosing. In ViDA, the dosing was chosen as it equated to approximately 3,000 IU per day which is the dose needed to raise 25-hydroxyvitamin D to 80–100 nmol/l. One study of topical

calcipotriol found a greater effect on inflammation in the epidermal rather than the dermal component of the skin (338). Therefore, a greater effect by vitamin D may be achieved in psoriasis by a topical rather than systemic route, by doses with a high concentration gradient across the epidermal/dermal barrier which is not achieved by oral administration. Additionally, perhaps calcipotriol may bind differently to the VDR compared with 1, 25 dihydroxyvitamin D_3 with a different physiological effect. It is known that the keratinocyte recruits inflammatory dendritic cells and the IL-17, producing T cells (136). Therefore, an epidermal effect could be important. An analogy is the use of topical and systemic steroids in the treatment of psoriasis. The topical steroid molecule can be altered, which changes the pharmacokinetics and pharmacodynamics of the molecule, altering the clinical effect. Calcipotriol is a synthetic analogue of vitamin D (190). Topical steroids are routinely used in the management of localised plaque disease. Used appropriately, they are considered safe and effective treatments but systemic steroids would not usually be used for chronic plaque psoriasis. There are no studies to compare the effect of systemic over topical steroids in psoriasis. It is the concern about rebound flares with systemic steroids, and instability of psoriasis, that provokes caution in their use. However, anecdotally, the use of a mid-strength topical steroid such as betamethasone valerate is far more effective when applied to a plaque of stable psoriasis compared with oral prednisone when it is given for a concomitant disease, so there are parallels here between oral and topical vitamin D preparations.

8.5 Psoriasis and Cardiovascular Risk

This is the first study in New Zealand to examine cardiovascular risk in a group of patients who have psoriasis. The recent meta-analysis in 2013 of cardiovascular risk in individuals with psoriasis noted that all but one of the studies reported were from European or North American populations, with the other being from Taiwan (2). The weight of evidence (see Chapter 4, Section 4.5) is that moderate to severe psoriasis, as measured by PASI or proxy measures such as treatments used, carries the greater risk of cardiovascular disease. The group in the ViDA study had mild disease as measured by their PASI with a mean (SD) of 3.1 (± 2.8). The participants in the ViDA study with psoriasis were found not to be at higher cardiovascular risk compared with the other participants. Mallbris et al (279) in Stockholm, Sweden, found no increased cardiovascular mortality among psoriatic outpatients (mild psoriasis) compared with the general population. Like the New Zealand NHI (see Chapter 5, Section 5.2.1), all Swedish patients have a unique identifier number which permits unambiguous linkage of information from different sources.

This is also the first study in New Zealand to examine arterial waveform in a group of patients with psoriasis and also to examine the largest number (n = 65) in an older age group, compared with the other two studies from Turkey (Table 48). Balta et al (326) did not report the PASI scores of their 35 patients with psoriasis. Sunbul et al examined 50 patients with psoriasis with a mean (SD) PASI of 13.7 (± 8.9). The “Psoriatic March” (see Chapter 4, Section 4.5.2) predicts that with greater systemic inflammation seen in severe psoriasis, greater endothelial dysfunction would occur. Therefore, it is reassuring that in the ViDA participants with mild psoriasis there was no difference in the two waveforms between those with and without psoriasis. The hypothesis is therefore supported. Sixty-five patients is a relatively small number so to avoid a type 2 error a larger study with greater numbers would be desirable.

Table 48: Comparison of three studies measuring arterial function in psoriasis

	Study		
Psoriasis patients	**Jarrett**	**Balta** (326)	**Sunbul** (327)
Patient numbers	65	32	50
Male/female	39/26	14/18	26/24
PASI	3.1 (± 2.8)	NG	13.7 (± 8.9)
Age years (SD)	65.5 (± 8.0)	34.6 (± 10.3)	43.3 (± 13.2)
BMI (kg/m^2) (SD)	28.8 (± 4.9)	25.2 (± 4.7)	27.2 (± 4.0)
Hypertension n (%)	23 (65)	NG	8 (16)
Diabetes mellitus n (%)	7 (11)	NG	4 (8)
Smoking n (%)	52 (80)	NG	10 (20)
Systolic blood pressure (mmHg) (SD)	137 (± 18)	117.8 (± 15.3)	123.8 (± 17.5)
Diastolic blood pressure (mmHg) (SD)	77 (± 11)	72.7 (± 10.0)	80.8 (± 12.2)
Augmentation index % (SD)	29.3 (± 12.5)	NG	25.8 (± 13.1)
Pulse wave velocity (m/s) (SD)	NG	7.63 (± NG)	6.78 (± 1.42)

NG = Not given.

8.6 Implications for Future Research

The first question for future research generated by this thesis is the cause of the high prevalence of cutaneous lupus in the Māori and Pacific population. 25-hydroxyvitamin D status has been found not to be a significant factor and therefore it is interesting to speculate on the reasons for the higher prevalence in these ethnic groups. For example, it would be particularly interesting to undertake a genetic analysis in Māori and Pacific people who have DLE, looking at polymorphisms of the ITGAM gene. Genome wide scans for autoimmune disease, including SLE, have been undertaken (339) and could also be considered comparing Māori and Pacific with European patients with cutaneous lupus.

The database that the thesis has generated, of patients with cutaneous lupus, already has permitted further research into cutaneous lupus including the paper, “Illness perception in association with psychological functioning in patients with discoid lupus erythematosus” (340).

A study to examine the adjunctive role of vitamin D supplementation in patients who have psoriasis, but are vitamin D deficient, would be difficult to undertake. It would require a multicentre study and with the advent of effective biologic agents would be difficult to justify.

An area that could be explored is the role of waveform measurement in New Zealanders with severe psoriasis (PASI > 10). The literature would support the view that they are likely to have a higher cardiovascular risk. It would be interesting to know if there were differences between ethnicities as well.

Chapter 9 Conclusion

The overarching theme of this thesis was to investigate aspects of the role of 25-hydroxyvitamin D in two dermatological diseases, namely cutaneous lupus and psoriasis. The main studies were the examination of the association of cutaneous lupus with 25-hydroxyvitamin D and the placebo-controlled study of the supplementation of vitamin D_3 (cholecalciferol) in patients with psoriasis. However, the two main studies led to two further substudies investigating the prevalence of cutaneous lupus and the cardiovascular risk of patients with psoriasis.

The findings of the systemic review were that:

- The prevalence of cutaneous lupus in Māori and Pacific people was not known. However, SLE, both in New Zealand and internationally, was more common in Māori and Pacific people and in people of darker skin.
- There have been no studies on the prevalence of cutaneous lupus in New Zealand.
- Only a few studies have examined the association of vitamin D status and cutaneous lupus. No studies have been undertaken with Māori and Pacific people in New Zealand.
- There are theoretical reasons why vitamin D may be useful in psoriasis but there are no published randomised controlled studies examining the clinical effect of vitamin D supplementation on psoriasis.
- There have been no studies of cardiovascular risk in patients with psoriasis derived from a New Zealand population.

The findings of the first study were that:

- Māori and Pacific people have a significantly greater age- and sex-adjusted risk of cutaneous lupus compared with the European population, with a relative risk of 2.47 (95% CI: 1.67–3.67).
- Māori and Pacific people have a significantly greater age- and sex-adjusted risk of DLE compared with the European population, with a relative risk of 5.96 (95% CI: 3.06–11.6).

The findings of the second study were that:

- Ethnic differences in 25-hydroxyvitamin D levels in Māori and Pacific people do not account for the increased relative risk of cutaneous lupus compared with the European population.
- The activity and the severity of cutaneous lupus are not related to 25-hydroxyvitamin D levels.

The findings of the third study were that:

- The addition of monthly vitamin D_3 100,000 IU (cholecalciferol) for 12 months does not alter the severity or quality of life of patients with mild psoriasis and therefore cannot be recommended as a therapeutic intervention.
- New Zealand patients with mild psoriasis are not at greater risk of cardiovascular disease than those without psoriasis.

The skin is essential in its role for the production of vitamin D through sun exposure. There is a complex interaction between modern day social behaviour and the need for sun exposure to generate sufficient vitamin D to maintain health and to avoid diseases associated with vitamin D deficiency. The VDR is ubiquitous, including expression in the keratinocyte, and therefore vitamin D must have a role. This thesis suggests that in respect of cutaneous lupus and mild psoriasis, there is not a significant role for vitamin D at a clinically detectable level.

Appendices

Appendix 1 Literature Search Strategy

All literature searches were done using Medline (Ovid SP) database and updated in August 2015. The strategies for the major literature searches are below.

a. Cutaneous lupus prevalence

1. Lupus Erythematosus, Cutaneous / Explode
2. /ep – Epidemiology, /eh – Ethnology
3. English Language, Humans
4. Maori/Maaori
5. Pacific
6. 1 and 4
7. 1 and 5
8. Incidence
9. Prevalence
10. 1 and 8
11. 1 and 9

b. Cutaneous lupus and Vitamin D

1. Lupus Erythematosus, Cutaneous/ Explode / Include all sub headings
2. Vitamin D, Explode / Include all sub headings
3. 1 and 2
4. Ultraviolet light/Explode/Include all sub headings
5. 1 and 4

c. Psoriasis and oral vitamin D

1. Psoriasis / Explode / Include all sub headings
2. Vitamin D/ Explode
3. 1 and 2
4. Humans and English Language

Appendix 2 GRADE Quality of Literature

GRADE approach to the level of quality of a body of evidence. Taken from "Cochrane Handbook for Systemic Reviews of Interventions" at http://handbook.cochrane.org/

The GRADE approach specifies four levels of quality (Table 12.2.a). The highest quality rating is for randomized trial evidence. Review authors can, however, downgrade randomized trial evidence to moderate, low, or even very low quality evidence, depending on the presence of the five factors in Table 12.2.b. Usually, quality rating will fall by one level for each factor, up to a maximum of three levels for all factors. If there are very severe problems for any one factor (e.g. when assessing limitations in design and implementation, all studies were unconcealed, unblinded, and lost over 50% of their patients to follow-up), randomized trial evidence may fall by two levels due to that factor alone.

Review authors will generally grade evidence from sound observational studies as low quality. If, however, such studies yield large effects and there is no obvious bias explaining those effects, review authors may rate the evidence as moderate or – if the effect is large enough – even high quality (Table 12.2.c). The very low quality level includes, but is not limited to, studies with critical problems and unsystematic clinical observations (e.g. case series or case reports).

Table 12.2.a: Levels of quality of a body of evidence in the GRADE approach

Underlying methodology	**Quality rating**
Randomized trials; or double-upgraded observational studies.	High
Downgraded randomized trials; or upgraded observational studies.	Moderate
Double-downgraded randomized trials; or observational studies.	Low
Triple-downgraded randomized trials; or downgraded observational studies; or case series/case reports.	Very low

Table 12.2.b: Factors that may decrease the quality level of a body of evidence

1. Limitations in the design and implementation of available studies suggesting high likelihood of bias.
2. Indirectness of evidence (indirect population, intervention, control, outcomes).
3. Unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses).
4. Imprecision of results (wide confidence intervals).
5. High probability of publication bias.

Appendix 3 Summary of CMDHB Population 2009

Summary of CMDHB population by age group and ethnicity (2009)

Age groups (years)	Māori	Pacific	Indian	Asian (exclude Indian)	European	Other (exclude European)	Total
00-04	12080	13090	3076	3504	7612	1838	41200
05-09	9510	11620	2631	3429	10176	2204	39570
10-14	8850	11000	2621	3929	10901	2149	39450
15-19	8310	10690	2255	4075	12492	2538	40360
20-24	6940	8800	2776	4214	9680	2290	34700
25-29	5310	7430	3764	3866	8720	2170	31260
30-34	5120	7370	3431	3309	9486	1794	30510
35-39	5340	7170	2758	3542	13927	2303	35040
40-44	4990	7050	2700	4730	14416	2134	36020
45-49	4440	5700	2607	4263	15552	2268	34830
50-54	3340	4480	2010	3250	14255	1795	29130
55-59	2620	3550	1402	2368	13075	1375	24390
60-64	1940	2890	1115	1635	12215	1185	20980
65-69	1230	1990	658	1342	9630	880	15730
70-74	740	1380	475	1005	6886	584	11070
75-79	410	860	253	577	5550	400	8050
80-84	140	480	107	293	4312	298	5630
85 +	70	240	78	182	3656	204	4430
Total	81380	105790	34717	49513	181839	29111	482350

Summary of CMDHB population by gender, age group and ethnicity (2009)

Female					
Age groups (Years)	Māori	Pacific	Indian	Asian (exclude Indian)	European
00-04	5870	6440	1482	1678	3689
05-09	4610	5650	1257	1703	4875
10-14	4320	5520	1244	1926	5384
15-19	4110	5270	1118	1922	6066
20-24	3690	4470	1457	2093	4402
25-29	2910	3940	1972	2048	4396
30-34	2850	3900	1793	1887	4935
35-39	2960	3790	1380	2150	7184
40-44	2700	3760	1331	2779	7285
45-49	2400	2970	1241	2409	7747
50-54	1800	2280	970	1800	7047
55-59	1420	1830	698	1272	6560
60-64	1010	1490	591	869	6163
65-69	690	1030	318	722	4871
70-74	420	750	258	522	3595
75-79	250	490	142	298	3000
80-84	80	280	66	164	2460
85 +	40	170	33	107	2465

Male					
Age groups (Years)	**Māori**	**Pacific**	**Indian**	**Asian (exclude Indian)**	**European**
00-04	6210	6650	1594	1826	3923
05-09	4900	5970	1374	1726	5301
10-14	4530	5480	1377	2003	5517
15-19	4200	5420	1137	2153	6426
20-24	3250	4330	1319	2121	5278
25-29	2400	3490	1792	1818	4324
30-34	2270	3470	1638	1422	4551
35-39	2380	3380	1378	1392	6743
40-44	2290	3290	1369	1951	7131
45-49	2040	2730	1366	1854	7805
50-54	1540	2200	1040	1450	7208
55-59	1200	1720	704	1096	6515
60-64	930	1400	524	766	6052
65-69	540	960	340	620	4759
70-74	320	630	217	483	3291
75-79	160	370	111	279	2550
80-84	60	200	41	129	1852
85 +	30	70	45	75	1191

Appendix 4 Type of Lupus by Ethnicity

Type of lupus by ethnicity

Ethnicity	ACLE	SCLE	DLE	Panniculitic
European/Pakeha	12	15	14	2
Pacific (all)	5	0	12	0
Māori	2	0	11	0
Indian	3	0	1	0
Asian	3	0	0	0
Total	25	15	38	2

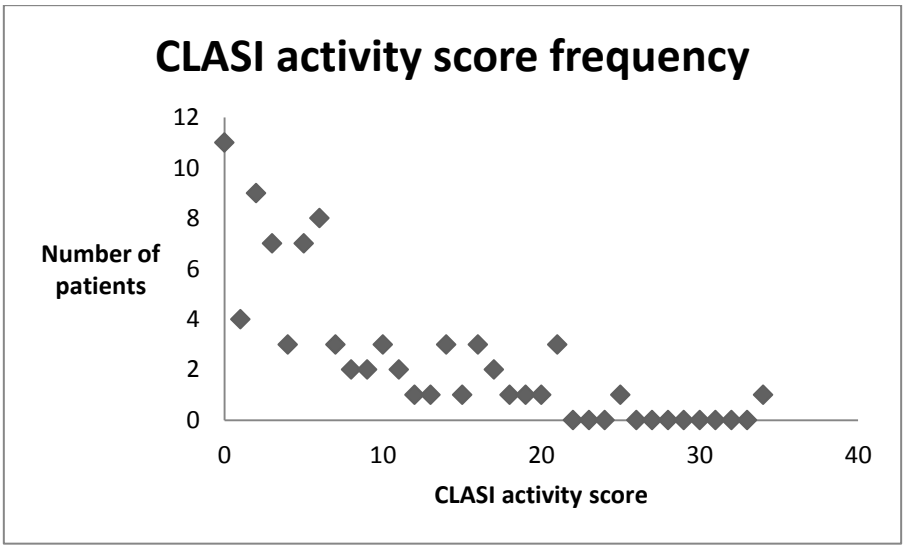
Appendix 5 Power Calculation

Power calculation for sample size for interventional study for the effect of vitamin D supplementation on cutaneous lupus.

The original intent of the thesis plan was to undertake a randomised, placebo-controlled study of the intervention of vitamin D to determine its effect on cutaneous lupus.

The patient group to be studied was to be the cohort identified in the prevalence study and to be eligible for an interventional study the patients needed to have pre-existing active cutaneous lupus. Sixty-nine patients out of the cohort of 80 patients were identified as having active cutaneous lupus. Most patients had low CLASI with a mean activity score of 8.5 (SD 6.9) leading to a right skewed distribution, therefore the data were log transformed for the power sample size calculation using PS: Power and Sample software (Vanderbilt University School of Medicine, Department of Biostatistics, Nashville, TN, USA).

CLASI Activity Score Frequency



To undertake an adequately powered study where clinically meaningful change in the activity of the cutaneous lupus was defined as a reduction in the CLASI score of 50% with a power of 0.9 and α of 0.05, each treatment group would need 37 patients. Therefore at least 74 patients with active lupus would be required to undertake this study.

The patient pool had different subtypes of cutaneous lupus and ideally only one subtype should be selected to undertake the proposed study which further reduced the numbers available.

The problem of insufficient patient numbers was discussed at length with the thesis supervisors and biostatistician. It was decided not to continue along this path for completion of the MD thesis but to switch to a similar study involving psoriasis rather than cutaneous lupus.

The proposed change was approved by the doctoral committee and the thesis retitled from “Cutaneous Lupus in Counties Manukau District Health Board” to “Skin Disease and Vitamin D”.

Appendix 6 DLQI

DLQI

Psoriasis Type: **«Service_Name»**

Score

Name:
Gender:
Date of Birth:

Age (Baseline):
Interview Date:
Interview Time: «Appointment_Start»

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 □

Appendix 7 PDI

PSORIASIS DISABILITY INDEX

- **Thank you for your help in completing this questionnaire.**
- Please tick one box for every question.
- Every question relates to the **LAST FOUR WEEKS ONLY.**

All questions relate to the LAST FOUR WEEKS.

DAILY ACTIVITIES:

1. How much has your psoriasis interfered with you carrying out work around the house or garden
   - **Very much** ❑
   - **A lot** ❑
   - **A little** ❑
   - **Not at all** ❑
2. How often have you worn different types or colours of clothes because of your psoriasis?
   - **Very much** ❑
   - **A lot** ❑
   - **A little** ❑
   - **Not at all** ❑
3. How much more have you had to change or wash your clothes?
   - **Very much** ❑
   - **A lot** ❑
   - **A little** ❑
   - **Not at all** ❑
4. How much of a problem has your psoriasis been at the hairdressers?
   - **Very much** ❑
   - **A lot** ❑
   - **A little** ❑
   - **Not at all** ❑
5. How much has your psoriasis resulted in you having to take more baths than usual?
   - **Very much** ❑
   - **A lot** ❑
   - **A little** ❑
   - **Not at all** ❑

- There are two different versions of questions 6, 7 and 8.
- If you are **at regular work or at school** please answer the first questions **6 - 8**.
- If you are **not at work or school** please answer the second questions **6 - 8**.

All questions relate to the LAST FOUR WEEKS.

WORK OR SCHOOL (if appropriate)

6. How much has your psoriasis made you lose time off work or school over the last four weeks?
   - **Very much** ❑
   - **A lot** ❑
   - **A little** ❑
   - **Not at all** ❑

7. How much has your psoriasis prevented you from doing things at work or school over the last four weeks?
   Very much ❑
   A lot ❑
   A little ❑
   Not at all ❑

8. Has you career been affected by your psoriasis? e.g. promotion refused, lost a job, asked to change a job.
   Very much ❑
   A lot ❑
   A little ❑
   Not at all ❑

IF NOT AT WORK OR SCHOOL: ALTERNATIVE QUESTIONS

6. How much has your psoriasis **stopped you** carrying out your normal daily activities over the last four weeks?
   Very much ❑
   A lot ❑
   A little ❑
   Not at all ❑

7. How much has your psoriasis **altered the way** in which you carry out your normal daily activities over the last four weeks?
   Very much ❑
   A lot ❑
   A little ❑
   Not at all ❑

8. Has your career been affected by your psoriasis? e.g promotion refused, lost a job, asked to change a job
   Very much ❑
   A lot ❑
   A little ❑
   Not at all ❑

All questions relate to the LAST FOUR WEEKS.

PERSONAL RELATIONSHIPS:

9. Has your psoriasis resulted in sexual difficulties over the last four weeks?
   Very much ❑
   A lot ❑
   A little ❑
   Not at all ❑

10. Has your psoriasis created problems with your partner or any of your close friends or relatives?
    Very much ❑
    A lot ❑
    A little ❑
    Not at all ❑

LEISURE:

11. How much has your psoriasis stopped you going out socially or to any special functions?
    Very much ❑
    A lot ❑
    A little ❑
    Not at all ❑

12. Is your psoriasis making it difficult for you to do any sport?

Very much	❑
A lot	❑
A little	❑
Not at all	❑

13. Have you been unable to use, criticised or stopped from using communal bathing or changing facilities?

Very much	❑
A lot	❑
A little	❑
Not at all	❑

14. Has your psoriasis resulted in you smoking or drinking alcohol more than you would do normally?

Very much	❑
A lot	❑
A little	❑
Not at all	❑

TREATMENT:

15. To what extent has your psoriasis or treatment made your home messy or untidy?

Very much	❑
A lot	❑
A little	❑
Not at all	❑

Please check that you have answered all the questions.

Thank you for your help.

Appendix 8 ViDA Psoriasis Questionnaire

Baseline Clinic Visit	Psoriasis Type:	**«Service_Name»**
1. Name:	Date of Birth:	
2. Age (Baseline):	Interview Date:	
3. Gender:	Interview Time:	

4. **Duration of psoriasis:**

Ask: ***"How long have you had psoriasis? By that I mean: how long ago did you first notice the rash?"***

Record answer: Years:

5. **Seasonal variation:**

Ask: ***"Does your psoriasis get worse at any particular time of year"?*** Y / N

If yes, ask: ***"When is that time"?***

Summer	1
Autumn	2
Winter	3
Spring	4

6. **Concomitant medication:**

Ask: ***"Are you on any other medication?"*** *Y / N*

I.	Beta blockers	Y / N
II.	Lithium	Y / N
III.	Systemic steroids	Y / N
IV.	Interferon	Y / N
V.	Antimalarials	Y / N
VI.	NSAIDs	Y / N
VIII.	Tetracyclines	Y / N
VIIII.	Name medication (*specify*)	

7. **Fitzpatrick skin type:**

Skin type	Typical Features	Tanning ability
I	Pale white skin, blue/hazel eyes, blond/red hair	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

8. **Type of Psoriasis:**

Chronic plaque	Y / N
Guttate	Y / N
Pustular	
Localised	Y / N
Generalised	Y / N
Scalp	Y / N
Flexural	Y / N
Nail	Y / N

---

9. **Physicians global assessment (PGA):**

Clear	0	
Almost Clear	1	
Mild	2	
Mild/moderate	3	=
Moderate	4	
Moderate severe	5	
Severe	6	

10. **Psoriasis Area and Severity Index (PASI) Score:** **=**

11. **Psoriasis Disability Index (PDI) Score:** **=**

12. **Dermatology Quality Life Index (DLQI) Score:** **=**

---

13. **Current Psoriasis Medication:**

Date(s): (DD/MM/YY)
Started

a. Topical:

Emollient Y / N

b. Topical Steroid 1:

Site on body used: _____

If Yes-Which class of steroid?

Class 1 (Very potent)	Y / N
Class 2 (Potent)	Y / N
Class 3 (Moderate)	Y / N
Class 4 (Mild)	Y / N

Name of topical steroid : _____

Date(s): (DD/MM/YY)
Started

c. Topical Steroid 2:

Site on body used: _____

If Yes-Which class of steroid?

Class 1 (Very potent)	Y / N
Class 2 (Potent)	Y / N
Class 3 (Moderate)	Y / N
Class 4 (Mild)	Y / N

Name of topical steroid : _____

d. Topical Steroid 3:

Site on body used: _____

If Yes-Which class of steroid?

Class 1 (Very potent)	Y/ N
Class 2 (Potent)	Y / N
Class 3 (Moderate)	Y / N
Class 4 (Mild)	Y / N

Name of topical steroid : _____

e. Coal tar	Y / N
f. Calcipotriol scalp lotion	Y / N
g. Calcipotriol cream/ointment	Y / N
h. Compounded mix *(Describe)*	Y / N

Describe compounded mix: _____

Date(s): (DD/MM/YY)
Started

i. Phototherapy:	Y / N
nUVB	Y / N
PUVA Systemic/Topical	Y / N
j. Systemic:	Y / N
Methotrexate	Y / N
Ciclosporin	Y / N
Acitretin	Y / N
k. Biologic:	Y / N
Adalimumab	Y / N
Etanercept	Y / N

Follow Up Clinic

«PID» Psoriasis Type:

1. Name: Date of Birth:
Age (Baseline): Interview Date:
Gender: Interview Time:

2. **Physicians global assessment (PGA):**

Clear	0	
Almost Clear	1	
Mild	2	
Mild/moderate	3	=
Moderate	4	
Moderate severe	5	
Severe	6	

3. **Psoriasis Area and Severity Index (PASI) Score:** **=**

4. **Psoriasis Disability Index (PDI) Score:** **=**

5. **Dermatology Quality Life Index (DLQI) Score:** **=**

---

6. **Concomitant medication:**

Ask: *"Have your medications changed?"* Y / N

		Date(s): (DD/MM/YY) **Started**	**Stopped**
Beta blockers	Y / N		
Lithium	Y / N		
Systemic steroids	Y / N		
Interferon	Y / N		
Antimalarials	Y / N		
NSAIDs	Y / N		
Tetracyclines	Y / N		
Name medication (*specify*)			

---

7. **Current Psoriasis Medication:**

Ask: *"Has your topical treatment changed since your last visit? By topical treatment I mean the creams that you use?"* Y / N

Date(s): (DD/MM/YY)

a. Topical: **Started** **Stopped**

Emollient Y / N

Steroid Y / N

b. Topical Steroid 1:

Site on body used: _____

If Yes-Which class of steroid?

Class 1 (Very potent) Y / N

Class 2 (Potent) Y / N

Class 3 (Moderate) Y / N

Class 4 (Mild) Y / N

Name of topical steroid : _____

Date(s): (DD/MM/YY)

Started **Stopped**

c. Topical Steroid 2:

Site on body used:_____

If Yes-Which class of steroid?

Class 1 (Very potent) Y / N

Class 2 (Potent) Y / N

Class 3 (Moderate) Y / N

Class 4 (Mild) Y / N

(Name of topical steroid :_____

d. Topical Steroid 3:

Site on body used:_____

If Yes-Which class of steroid?

Class 1 (Very potent) Y / N

Class 2 (Potent) Y / N

Class 3 (Moderate) Y / N

Class 4 (Mild) Y / N

(Name of topical steroid :_____

e Coal tar Y / N

f. Calcipotriol scalp lotion Y / N

j. Calcipotriol cream/ointment Y / N

k. Compounded mix *(Describe)* Y / N

(Describe compounded mix:_____

Ask*:* *"Have you had any phototherapy since your last appointment? By that I mean light treatment."* Y / N

		Date(s): (DD/MM/YY)	
Phototherapy:		**Started**	**Stopped**
nUVB	Y / N		
PUVA Systemic/Topical	Y / N		

Ask: *"Have you started/changed your systemic treatment? By that I mean your tablets or injections."* Y / N

		Date(s): (DD/MM/YY)	
Systemic:		**Started**	**Stopped**
Methotrexate	Y / N		
Ciclosporin	Y / N		
Acitretin	Y / N		
Biologic:			
Adalimumab	Y / N		
Etanercept	Y / N		

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