Environmental ultraviolet-B exposures and measured health outcomes in English children

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Abstract

Purpose

Vitamin D status has been shown to significantly impact extra-skeletal health outcomes. In the UK, the ability of the population to synthesize vitamin D is highly sensitive to environmental factors including ultraviolet-B wavelength light. This thesis aims to investigate the impact of environmental determinants of vitamin D status on child population health. Asthma, lower respiratory tract infection (LRTI) and gastroenteritis admission rates in English children will be analysed with meteorological variables at multiple geographical levels.

Methods

Five ecological studies were carried out. Three sets of multivariate linear regression analyses were performed to examine the associations between regional meteorological variables (hours of sunshine, rainfall and air temperature) and admission rates of asthma, LRTI and gastroenteritis in children in England between 2002 and 2011. Regional income deprivation affecting children index (IDACI) scores were used to control for population socioeconomic deprivation. Met Office and NHS Hospital Episode Statistics (HES) datasets were matched to create variables in these models. Extended generalised estimating equations were also used to explore these relationships. The remaining two studies focused on the relationships between acute paediatric asthma and LRTI admission rates on a GP-practice level, and ultraviolet-B (UVB) radiation doses in England between 2013 and 2018. HES admission data and Tropospheric Emission Monitoring Internet Service (TEMIS) satellite data on UVB levels of wavelengths specific to the vitamin D action spectrum (D-UVB) were used to carry out multivariate linear regression models on a GP and Clinical Commissioning Group aggregate

levels. Maternal smoking rates, GP practice IDACI scores, latitude, longitude, age and gender were also included in these models.

Results

The average English child population from 2002 to 2011 in the first three sets of analyses was 9,731,440, with average admission rates of 265.3 per 100,000 per annum, 390.0 per 100,000 per annum and 1375 per 100,000 per annum for paediatric asthma, LRTI and gastroenteritis respectively. Asthma, LRTI and gastroenteritis admission rates were found to be significantly inversely associated with hours of sunshine (HoS) ($p<0.001$). In the linear regression analyses, total annual rainfall and average temperature in English regions were also significantly associated with LRTI and gastroenteritis admissions ($p<0.001$). Regional IDACI scores were found to be significantly associated with asthma and LRTI admissions. In the studies focusing on D-UVB levels and child health, between 2013 and 2018 the average asthma admission rate was 314 per 100,000 per annum, and the average LRTI rate between 2016 and 2019 was 678 per 100,000 per annum. The average D-UVB levels corrected for cloud cover between 2013 and 2018 was 794.98 kJ/m^2. Both asthma and LRTI admission rates were found to be significantly associated with cloud-corrected D-UVB levels ($p<0.001$) at both GP and CCG levels. There were varying associations between asthma and LRTI admission rates and the other covariates included in these models.

Conclusions

Meteorological factors were associated with hospital admission rates for common paediatric conditions; the most reliably significant factor associated with a decrease in admissions was

hours of sunshine or D-UVB levels. These findings support the hypothesis that population vitamin D status has a significant influence on child health, and that targeting this with encouraging judicious sunlight exposure, outdoor activity, weight loss or a comprehensive supplementation programme could be effective preventative measures.

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List of abbreviations

$1,25(OH)_2D$	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
7-DHC	7-dehydroxycholesterol
CCG	Clinical Commissioning Group
DBP	Vitamin D-Binding Protein
ESA	European Space Agency
FGF23	Fibroblast growth factor 23
GEE	Generalised estimating equation
GOME	Global Ozone Monitoring Experiment
GP	General Practice/Practitioner
HES	Hospital Episode Statistics
HoS	Hours of sunshine
ICD-10	International Classification of Disease (10^{th} Edition)
ICS	Inhaled corticosteroid
IDACI	Income Deprivation Affecting Children Index
IFN	Interferon
IL	Interleukin
iNOS	Inducible nitric oxide synthase
IOM	Institute of Medicine
iTreg	Inducible T-regulatory cell
LA	Local Authority
LRTI	Lower respiratory tract infection

MHC	Major histocompatibility complex
NCX1	Sodium-calcium exchanger
NDNS	National Diet and Nutrition Survey
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHS	National Health Service
NNT	Number needed to treat
NSP	Non-structural protein
OMI	Ozone monitoring instrument
ONS	Office for National Statistics
PCT	Primary Care Trust
PMCA	Plasma membrane Ca^{2+} ATPase
PTH	Parathyroid hormone
RANKL	Receptor activator of nuclear factor kappa-B ligand
RCT	Randomised Controlled Trial
RSV	Respiratory syncytial virus
RXR	Retinoid X receptor
SATOD	Smoking at time of delivery
SCIAMACHY	Scanning Imaging Absorption spectrometer for Atmospheric Chartography
SHA	Strategic Health Authority
SZA	Solar zenith angle
TEMIS	Tropospheric Emission Monitoring Internet Service
TGF	Tissue growth factor
TLR	Toll-like receptor

TNF	Tumour necrosis factor
TRPV	Transient receptor potential cation channel subfamily V
UVB	Ultraviolet-B
VDR	Vitamin D receptor
VDRE	Vitamin D response element
WHO	World Health Organisation

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I would like to thank Dr Benjamin Davies who originally published the paper on asthma and hours of sunshine. This was very much the starting point of my thesis and my research follows where the research team led. I would like to thank Guy Thompson, Director of Respiratory Health Outcomes at GSK, for kindly helping me in obtaining the more recent NHS Hospital Episode Statistics datasets through Health iQ. I would like to thank Prof Lina Zgaga for the invaluable help in allowing us to focus this project on vitamin D by providing us with ultraviolet-B radiation data. I would like to thank Dr Jos van Geffen for helping with my understanding of the UVB variables and thus improving the quality of my writing.

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Aims and Objectives

This thesis aims to investigate the impact of hours of sunshine and/or ultraviolet-B wavelength radiation on three markers of child health in the UK: hospital admissions for asthma, lower respiratory tract infection and gastroenteritis. The effects of environmental factors on disease in a large population will be examined, including hours of sunlight and UVB levels, as well as how vitamin D can impact paediatric conditions modulated by the immune system.

Firstly, the associations between annual hospital admissions of children with common paediatric pathologies and annualised meteorological variables such as hours of sunlight, temperature and rainfall will be investigated. A confirmatory statistical analysis of asthma admissions and weather variables will be performed using a previously validated methodology. Analyses will then be undertaken for lower respiratory tract infection (LRTI) and gastroenteritis admissions using the same process.

Next, using more recent data, the relationship between UK paediatric asthma and LRTI admission rates and UVB radiation levels will be explored. These analyses will look at admissions data from both GP practice and CCG levels, as well as UVB radiation levels specifically of wavelengths that vitamin D is most efficiently synthesized, corrected for attenuation by cloud cover. The results of the analyses should together give a view of the presence and magnitude of the effect the environment has on adequate vitamin D status in UK children, and in turn the common paediatric conditions linked to vitamin D deficiency.

1 Literature review

A vitamin is an organic compound essential for normal growth and nutrition that the human body cannot synthesize endogenously (1). While all vitamins can be obtained through diet, vitamin D is exceptional to the classical definition of a vitamin, as under certain environmental circumstances it can be biologically synthesized (2). Hormones are regulatory chemicals produced by the body to control physiological processes in tissues and organs. Vitamin D is a prohormone; it requires enzymatic activation before becoming biologically active. When activated, it is a powerful downstream effector hormone, directly impacting gene transcription for many biological processes in multiple organ systems (3). Physiological mechanisms to tightly regulate the homeostasis of vitamin D status have evolved over time, since before organisms developed calcified skeletons. Vitamin D deficiency, with its environmental and genetic predictors, has wide-ranging effects on the body. It is important to explore the metabolism and mechanisms of action of vitamin D to explain these effects.

1.1 Vitamin D synthesis and metabolism

1.1.1 Chemical properties of vitamin D

Vitamin D, also known as vitamin D_3 or cholecalciferol, has the chemical formula $C_{27}H_{44}O$ (4). Unlike cholesterols, from which it is derived, vitamin D has three hydrocarbon rings and only one hydroxyl group is attached to the third carbon atom in the first ring, unlike its steroid hormone relatives (Figure 1.1). The molecule has different chemical groups with different polarities that are water soluble and insoluble, making vitamin D amphiphilic. The hydrophilic functional group can overcome polar energy barriers, allowing vitamin D to enter cell plasma membranes (5). When drawn into the phospholipid bilayer, its hydrophobic

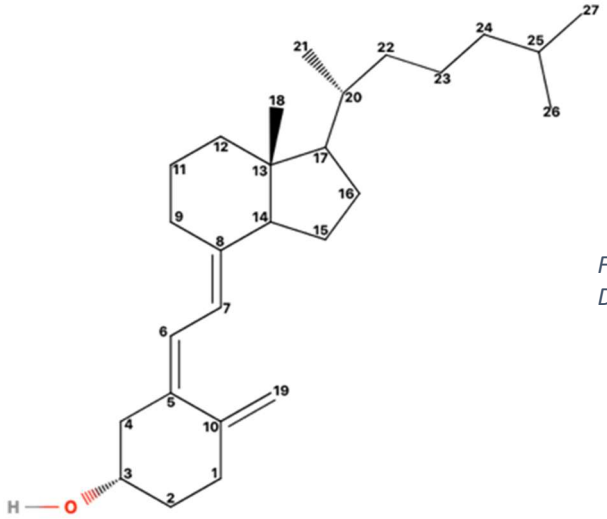

Figure 1.1- Skeletal formula of cholecalciferol (vitamin D3) drawn using molview (290)

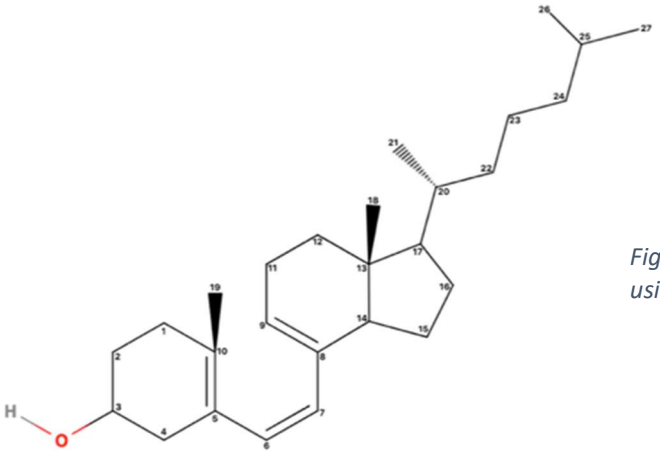

Figure 1.2- Skeletal formula of pre-vitamin D3, drawn using molview (290)

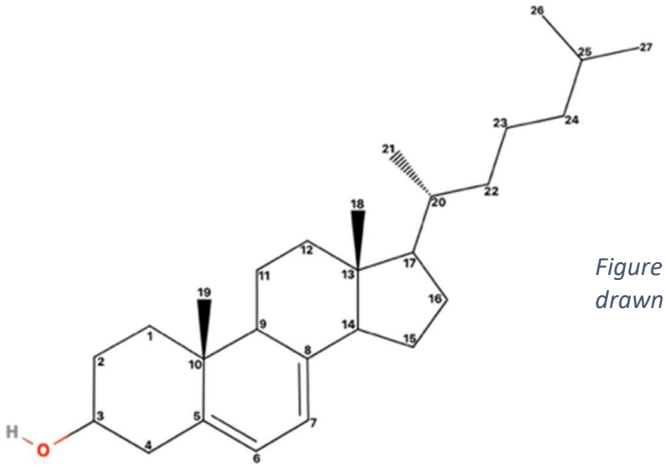

Figure 1.3- Skeletal formula of 7-dehydroxycholesterol drawn using molview (290)

aliphatic chain repels the hormone out of the membrane and into the intracellular space. The more hydrophilic hydroxyl groups added to the molecule, the better it diffuses between extra- and intra-cellular compartments. When enzymatically activated, hydroxyl groups can be found in the 1- and 25- carbon positions on the molecule, and when excreted, a further hydroxyl group is added to the 24- carbon position.

1.1.2 Where do we get vitamin D from?

Most humans gain only a small proportion of their vitamin D from dietary sources. Endogenous synthesis of vitamin D begins in the skin (Figure 1.4). The chemical precursor to vitamin D, 7-dehydroxycholesterol (7-DHC) (Figure 1.3), is located in keratinocytes, especially in the stratum spinosum and stratum basale of the epidermis (6). Converted from cholesterol using 7-dehydrochlesterol reductase (7), this compound is a steroid alcohol, or sterol, and resides principally within cell phospholipid membranes. When skin is exposed to sunlight, ultraviolet-B (UVB) radiation can provide the necessary activation energy for the conversion of 7-DHC to pre-vitamin D_3. This intermediate compound (Figure 1.2) is created when UVB radiation reaches the 7-dehydroxycholesterol molecules and breaks the single bond between the 9th and 10th carbon atoms. In a pale-skinned Caucasian individual, it is estimated that 30 minutes of sunlight exposure on the face and forearms alone is enough to generate 2000 IU of vitamin D (8).

The optimum wavelength of solar rays required to catalyse the production of pre-vitamin D is between 290-315nm beyond the range of visible light (9). This is a chemically unstable intermediate compound, which undergoes an endothermic structural isomerisation reaction, forming 5,6-trans-cholecalciferol (10) (8). Vitamin D_3 can be inactivated by the same UVB

radiation exposure, reversibly producing lumisterol and tachysterol (11). Therefore, vitamin D_3 production is a somewhat self-limiting process; nevertheless, it is extremely efficient due to the vast surface area of the skin (12). This form of vitamin D can be referred to as a secosteroid, meaning it resembles a steroid hormone but for a broken aromatic ring.

Another source of vitamin D for the body is intestinal absorption of dietary cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). Vitamin D_2 is derived at first from fungi and plants converting ergosterol via ultraviolet radiation (13), and as a fat-soluble vitamin, it is stored in fat droplets in animals' adipose tissue. Therefore, dietary vitamin D is best obtained via the consumption of oily fish and dairy products, as well as eggs and red meat (14) (15). Structurally similar to cholecalciferol, it differs by a double bond between the 22nd and 23rd carbon atoms, in addition to an extra methyl group attached to the 24th (14).

Absorbed in the jejunum with digested fats, vitamin D_2 is transported in chylomicrons from intestinal villi lacteals through the lymphatic system, before entering the venous system where the thoracic duct meets the venous angle (at confluence of left internal jugular and left subclavian veins) (16).

1.1.3 Transport and metabolism of vitamin D

Whether derived from the skin or absorbed via the jejunum, vitamin D is transported in the bloodstream via the vitamin D binding protein (DBP) (16). Binding many vitamin D metabolites, this protein plays a vital role in the endocrine activities of vitamin D (7) (17). Transport and cellular uptake of vitamin D is enhanced by megalin-mediated endocytosis of the DBP itself, a mechanism evolved to ensure diffusion of vitamin D directly into target cells

for enzymatic conversion or otherwise (Figure 1.5) (18). Cholecalciferol is stored in adipocytes, as it is fat-soluble, and these stores can be mobilised in times of reduced vitamin D availability. Consequently, vitamin D has a lower bioavailability in individuals with more adipose tissue. Obese individuals may be more predisposed to lower serum levels of circulating vitamin D due to large reservoirs of less accessible vitamin D (19).

The first stage of vitamin D activation occurs in the liver. Cholecalciferol and ergocalciferol are hydroxylated at the 25-carbon position by cytochrome P450 enzymes CYP2R1, CYP27A1 or CYP3A4 (also known as 25-hydroxylases) which are found on hepatocytic rough endoplasmic reticula (20). The newly formed 25-hydroxyvitamin D (25(OH)D), transported by the vitamin D binding protein, enters the bloodstream as a stable intermediate metabolite of vitamin D. With a biological half-life of around 15 days and influenced more by long-term vitamin D_2 or D_3 availability than other short-term endocrine fluctuations, it is usually a good biomarker for overall vitamin D status

The kidneys are the major site of fully activated vitamin D production. Mitochondria in the epithelial cells of the proximal convoluted tubule contain the cytochrome P450 enzyme CYP27B1 (also known as 1-α hydroxylase), which adds a second hydroxyl group onto the 1st carbon atom in the vitamin D molecule (21). Biologically active vitamin D, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), created by this multi-organ production chain, is released into the bloodstream, bound to the DBP (22). CYP27B1 activity is upregulated by parathyroid hormone and downregulated by fibroblast growth factor 23 (FGF23) and $1,25(OH)_2$-vitamin D itself (20).

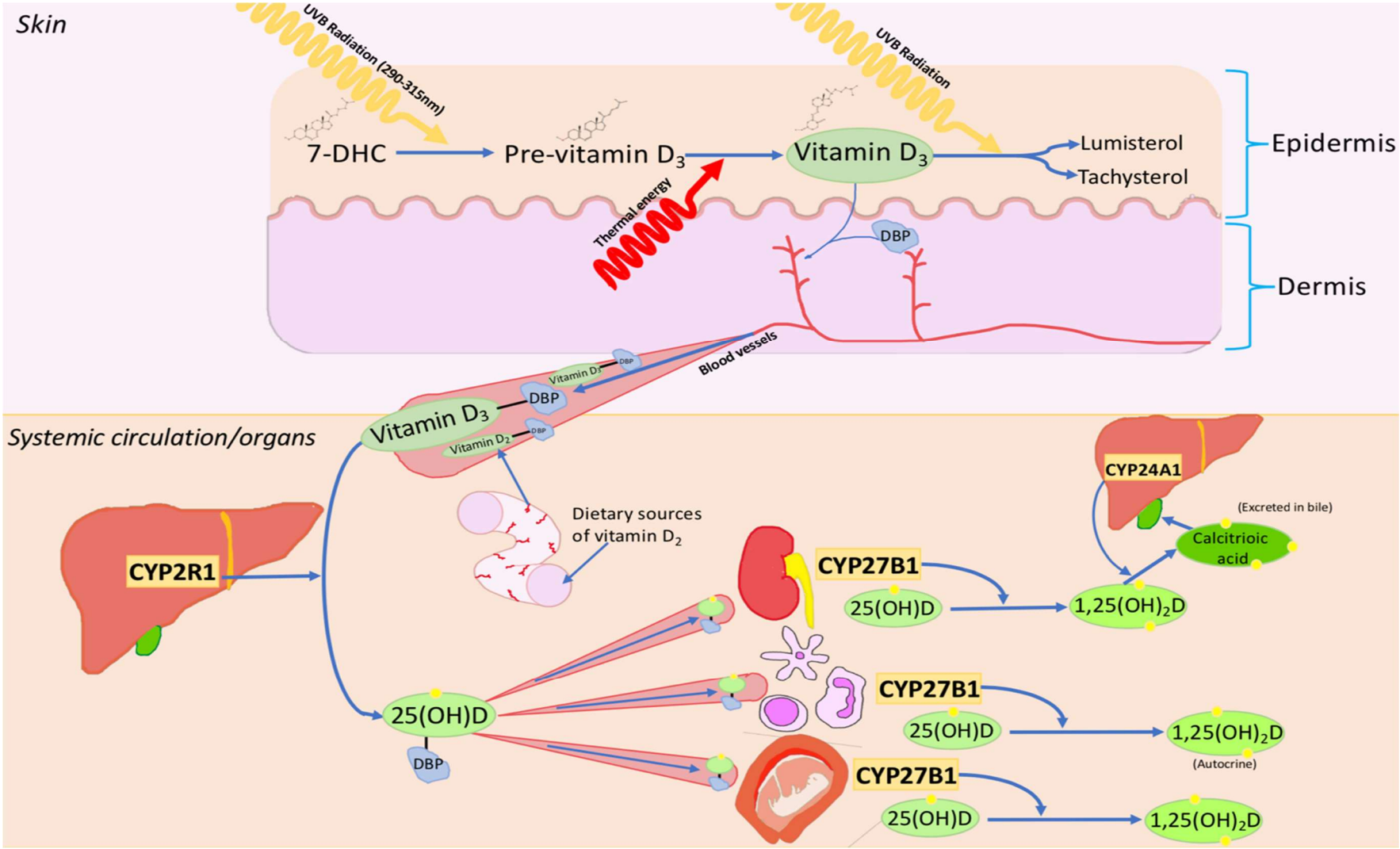

Figure 1.4- Synthesis and metabolism of vitamin D.

This illustration depicts: vitamin D's conversion from 7-dehydroxycholesterol (7-DHC); binding and transport on the vitamin D-binding protein (DBP); metabolism forming its stable intermediate 25-hydroxyvitamin D (25(OH)D) and the biologically active 1,25-dihydroxyvitamin D (1,25(OH)2D); hepatic conversion and biliary excretion of the inactive calcitrioic acid.

The kidneys are not the only site of enzymatic activation of vitamin D, extra-renal conversion occurs in immune cells such as macrophages, dendritic cells and lymphocytes (23). Excretion of both $1,25(OH)_2D$ and 25(OH)D is made possible by 24-hydroxylation of the molecule, carried out by mitochondrial CYP24A1 (20). The $24,25(OH)_2D$ or $1,24,25(OH)_3D$ (calcitroic) acid that is formed is excreted in bile (24).

1.2 Physiological actions of vitamin D

1.2.1 Vitamin D as an important genomic regulator

Vitamin D interacts with cells in a similar way to its corticosteroid cousins. When this secosteroid hormone travels into cells, either via diffusion through phospholipid membranes or endocytosis of the vitamin D binding protein, 1,25-dihydroxyvitamin D diffuses through the nuclear envelope and binds to the nuclear vitamin D receptor (VDR) (20) (25). This active form of vitamin D has wide-ranging effects on the genome, with the vitamin D receptor distributed across many different cells and tissues (26). The VDR is a chromatin-derived protein with high-affinity vitamin D and DNA binding domains (27). When bonded to its ligand, the VDR heterodimerizes with the retinoid X receptor (RXR) to exert its transcriptional potential (25).

Vitamin D response elements (VDREs) are the targets of this receptor-ligand complex, where the vitamin D-VDR-RXR complex recruits other co-activator or co-repressor complexes, and accordingly acts as a transcription factor in order to trans-activate or trans-repress specific genes (25) (27).

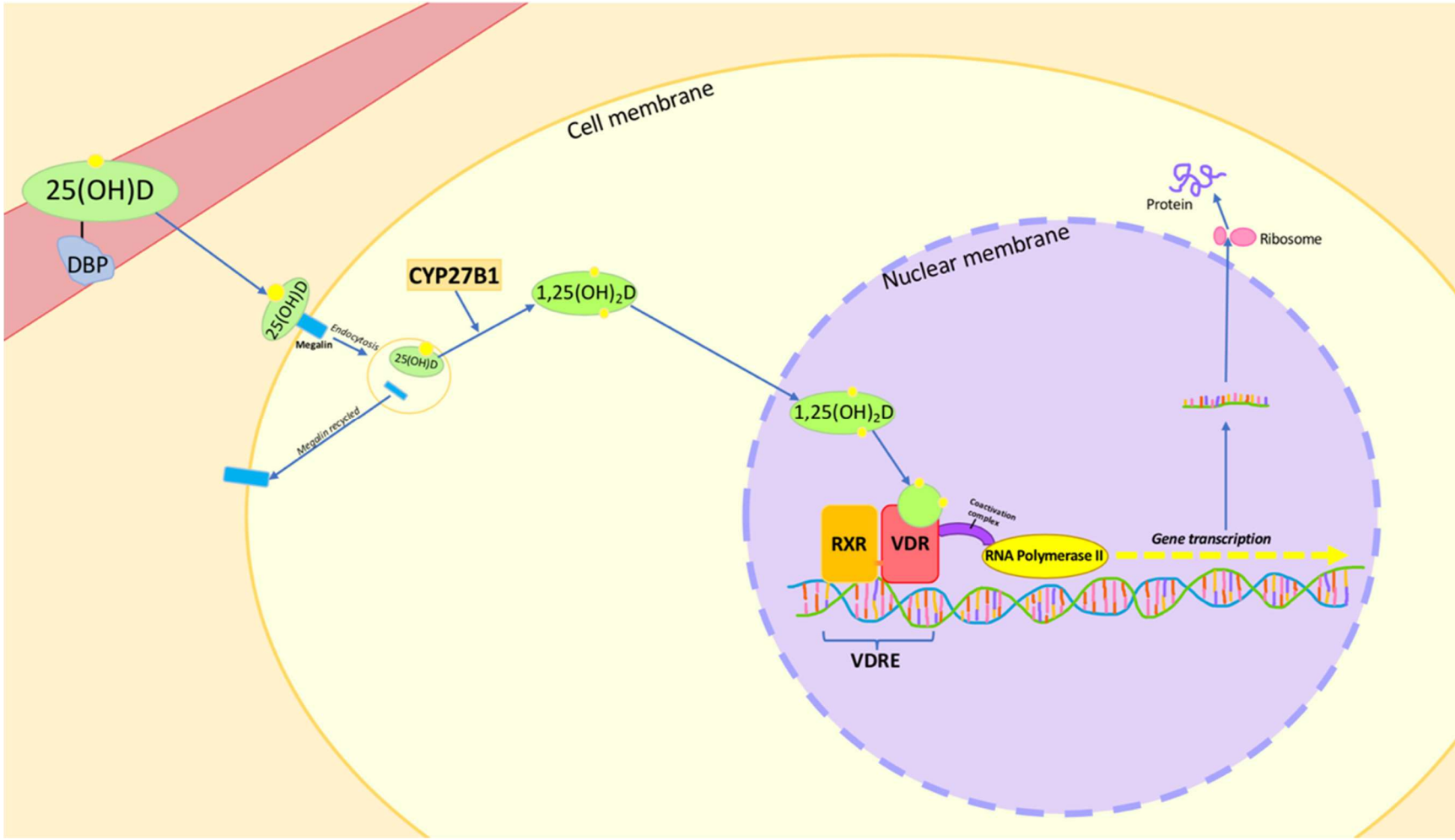

Figure 1.5- Cellular uptake and nuclear actions of vitamin D.

25-hydroxyvitamin D (25(OH)D) is activated intracellularly, travels to the nucleus where it binds to the vitamin D receptor (VDR), which forms a complex with the retinoid-X receptor (RXR) to target vitamin D response elements (VDRE).

Activated vitamin D influences processes such as bone metabolism, intestinal and renal electrolyte absorption or reabsorption, cell cycle control and immunity (25) (28).In addition to its direct genetic actions on cell nuclei, vitamin D has indirect epigenetic effects, with the upregulation of enzymes able to activate or repress many genes via DNA histone modification (29). It has been estimated that vitamin D has the potential to affect around 5% of the genome (30). Researchers have only recently started to understand the implications of this on extra-skeletal body systems (3).

1.2.2 The keystone of calcium homeostasis

Vitamin D is well known to be the essential to the endocrine pathway controlling calcium homeostasis. It ensures adequate bone mineralisation as well as calcium absorption from the duodenum and its reabsorption from the distal convoluted tubules in the kidney (28). In duodenal enterocytes, 1,25-dihydroxyvitamin D acts upon VDREs coding for the upregulation of luminal expression of the transient potential vanilloid type 6 (TRPV6) calcium channel (Figure 1.6) (25). Vitamin D-deficient individuals are only able to absorb 10-15% of calcium compared to when sufficient (19) (31). Ca^{2+} ions are then bound to intracellular calbindin, whereupon basolateral extrusion into the bloodstream occurs via the plasma membrane Ca^{2+} ATPase (PMCA), increasing serum Ca^{2+} concentration (27) (32).

A more sensitive mechanism of increasing serum calcium concentration is through the action of the parathyroid glands and their secretion of parathyroid hormone (PTH) (4). Parathyroid chief cells monitor calcium content of the blood and respond to low calcium levels by secreting PTH (4) (33). This hormone accelerates the renal activation of vitamin D, thereby enhancing calcium absorption and retention. This process is controlled in a negative

feedback loop by chief cells' VDR expression, downregulating PTH production in high concentrations of 1,25-dihydroxyvitamin D (25). Vitamin D works synergistically with PTH when acting on osteoblast cells, upregulating production of the cytokine RANK-ligand, which acts on pre-osteoclasts triggering their maturation into osteoclasts (Figure 1.6) (27). Osteoclasts then bind to bone, releasing H^+ ions, collagenases such as cathepsin K, and matrix metalloproteinases, which act to resorb minerals from bone tissue (34). The harvested calcium (Ca^{2+}) and phosphate (PO_4^{3-}) ions then enter the bloodstream, preserving homeostasis of these electrolytes.

Renal calcium retention is also modulated by PTH and $1,25(OH)_2D$. In the distal convoluted tubule of nephrons, calcium is actively transported into the tubular epithelial cell via the TRPV5 channel, a process regulated by the actions of activated vitamin D on the VRDEs of the cell nuclei (27). The mechanism of transporting the now intracellular calcium ions into the bloodstream in renal tubular epithelial cells reflects the process in enterocytes (Figure 1.6). Calbindin carries Ca^{2+} ions to the sodium/calcium exchanger (NCX1) on the cell's basolateral membrane for them to enter renal blood vessels (27).

While phosphate (PO_4^{3-}) ions are principally absorbed in the intestine paracellularly and thus independently of $1,25(OH)_2$ vitamin D, the reabsorption of PO_4^{3-} ions in the kidneys is influenced significantly by active vitamin D (25). Sodium-dependent phosphate co-transporters (Npt2a and Npt2c) are upregulated by the vitamin D transcription complexes and reabsorb phosphate ions into the circulation (25) (35)..

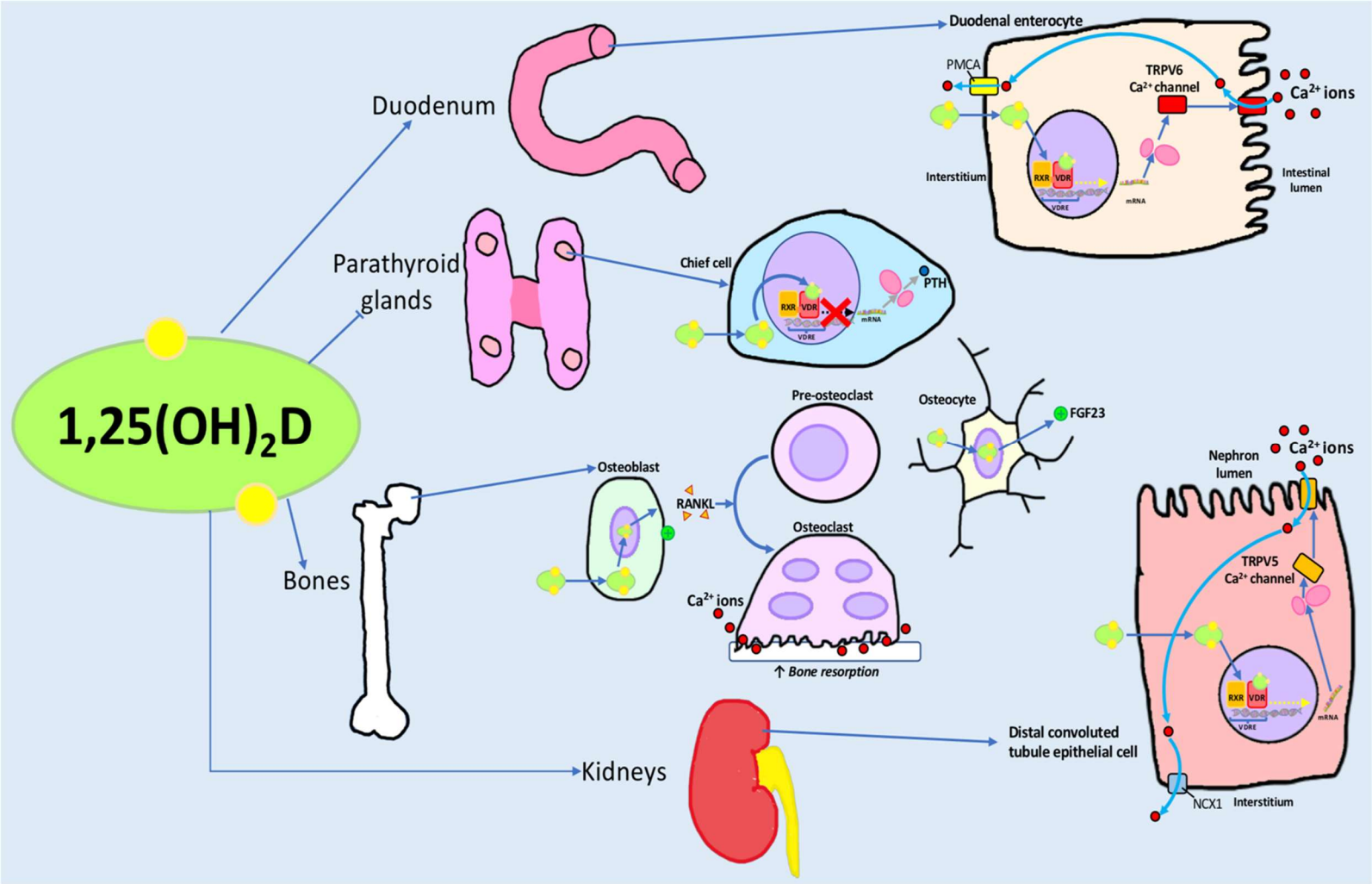

Figure 1.6- Multi-system targets of vitamin D in the context of calcium homeostasis

This is counter-acted by FGF23, a hormone secreted by osteocytes and osteoblasts in response to raised serum $1,25(OH)_2$ vitamin D, which reduces reabsorption of PO_4^{3-} ions, increasing the PO_4^{3-} concentration of urine (36)

1.2.3 Extra-skeletal effects of vitamin D

The actions of 1,25(1OH)2D on calcium metabolism are well-documented and understood, but only recently have extra-skeletal effects of vitamin D on the immune system been researched (30). Most body tissues have been shown to express the vitamin D nuclear receptor (28) (37). It acts on a plethora of immune cells, via nuclear VDR upregulation of regulatory or anti-inflammatory cytokine gene transcription, or repression of pro-inflammatory cytokine expression. It has been shown that monocytes and macrophages express their own 1-hydroxylase enzymes, meaning they are particularly responsive to changes in 25[OH] vitamin D levels (38). Macrophages have also been shown to upregulate the expression of 1α-hydroxylase in response to toll-like receptor antigenic ligation (39). Renal activation of vitamin D, however, remains the only process to affect systemic serum 1,25-dihydroxyvitamin D concentrations, with the notable exceptions of the placenta and activated macrophages as seen in sarcoidosis (37). Extra-renal production of activated vitamin D is for the purposes of autocrine or paracrine signalling in the presence of 25(OH)D, unlike the systemic effects of the endocrine production pathway previously outlined (38) (40).

1.2.3.1 Effects on the innate immune system

Vitamin D has several immunomodulatory effects, influencing different aspects of the immune system (Figure 1.7). Peptides such as defensins and cathelicidin strengthen

antimicrobial defence and are produced at higher rates by monocytes and macrophages when 1,25$(OH)_2$D transcription complexes target the VDREs on genes which code for their expression (41) (42) (43).

The transcription factor, nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), is activated in macrophages and their precursors monocytes by inflammatory stimuli, leading to the release of pro-inflammatory cytokines tumour necrosis factor alpha (TNF), interleukin (IL)-1 and IL-6, in addition to the chemotactic agent CXCL8 (44). Vitamin D suppresses this process by upregulating the production of inhibitor kappa B [IκB], a potent inhibitor of NFκB, thereby reducing macrophage inflammatory responses and amplifying chemotaxis of neutrophils (42) (44).

Autophagy is also upregulated in macrophages, the process by which immune cells internally catabolise cellular components and suppress inflammation (45) (46). Vitamin D also modulates immune responses of innate immune cells through reactive oxygen species production, via activation and inhibition of inducible nitric oxide synthase (iNOS) in order to enhance or suppress the effects of inflammation on surrounding tissues (42).

1.2.3.2 Effects on the adaptive immune system

Dendritic cells, the bridge between the innate and adaptive immune systems, are also affected by 1,25$(OH)_2$D (27). There is a reduced expression of the antigen presenting class II major histocompatibility complex (MHC II) and its costimulatory molecules, altogether dampening adaptive immune system responses (Figure 1.7) (27) (47).

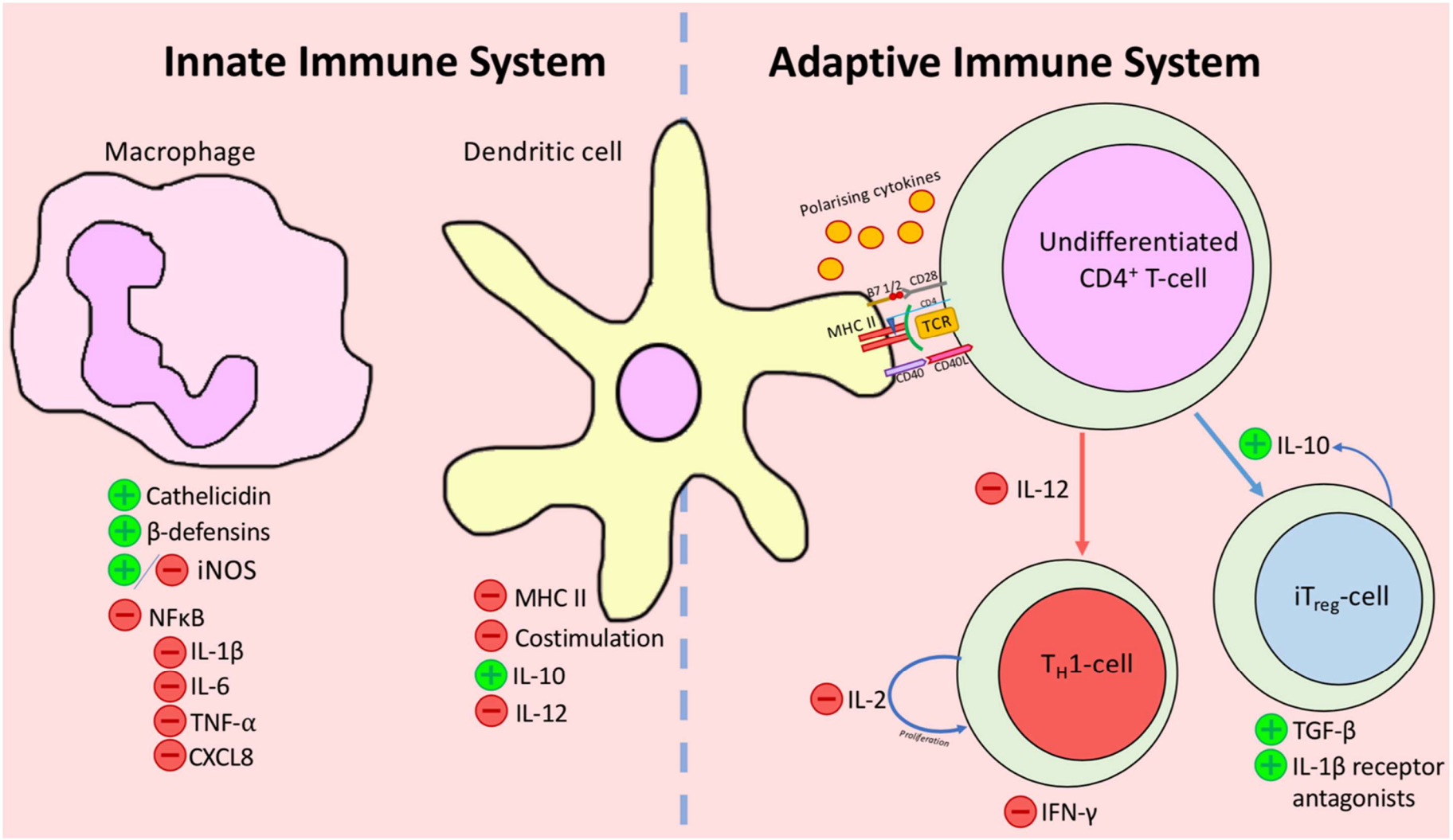

Figure 1.7- Effects of vitamin D on the innate and adaptive immune systems

Vitamin D's effects on dendritic cell phenotype also leads to the increased production of interleukin (IL)-10, which in turn differentiates $CD4^+$ T-cells into inducible regulatory T-cells (iT_{reg}) (via the transcription factor FoxP3) (48). These T_{reg} cells then mitigate inflammatory immune responses by secreting IL-1 receptor antagonists, tumour growth factor-beta (TGF-β) and further IL-10 (49). Influenced by $1,25[OH]_2D$, dendritic cells also reduce transcription of IL-12, which polarizes $CD4^+$ T-cell differentiation towards a pro-inflammatory, T-helper 1 (T_H1) phenotype. T_H17 cell differentiation is also repressed, which would otherwise serve to propagate chronic inflammatory processes (50). While vitamin D broadly serves to activate the cells of innate immune system and suppress adaptive immunity, this generalisation does not extend to its influence on dendritic cells, the pivotal bridge between the two aspects of immunity- instead its actions are more complex, selectively favouring and impeding certain immune processes and cell lineages (51). Its co-stimulatory actions are suppressed, while at the same time the cells' movement through the lymphatic system remains unimpeded, and specific phenotypical activities are stimulated (27) (49).

Compounding these upstream effects on dendritic cells, lymphocytes are also directly impacted by raised $1,25(OH)_2D$ levels (49). Vitamin D has stimulatory effects on T-cell production of IL-2, a cytokine responsible for proliferation in response to T-cell activation, binding to autocrine receptors; this modulates the adaptive immune response, inhibiting proliferation dilutes the magnitude of this process considerably (42) (52). Transcription of genes coding for the expression of interferon gamma (IFN-γ), TNF-α, IL-17 and IL-21 are also suppressed. This favours T-cell maturation into less inflammatory phenotypes while directly limiting their inflammatory cytokine secretion, diminishing long-term inflammatory processes (Figure 1.7) (42) (50). The abundance of the VDR in T-cells also leads to activated

vitamin D being able to drive expression of the transcription factors GATA-3 and FoxP3, which makes the T-cells more responsive to cytokine stimuli from dendritic cells encouraging differentiation into T-helper-2 and T-regulatory phenotypes (42) (53).

1.3 Defining and measuring vitamin D deficiency

The importance of vitamin D to health becomes apparent when the effects of deficiency are explored. Vitamin D deficiency was so crucial to the humans first migrating from Africa to Europe that they evolved to reduce the concentration of melanin in their skin, making vitamin D photosynthesis far more efficient (54). The environmental factor driving this natural selection process was the reduced availability of UVB radiation needed to produce vitamin D the further north humans migrated, an environmental factor which affects populations at higher latitudes today (54).

1.3.1 Classifying vitamin D status

Deficiency in the UK is officially defined as serum 25-hydroxyvitamin D <25 nmol/L, the point below which musculoskeletal symptoms usually manifest in patients (55) (56). However, there has been a recent discussion over the concept of insufficiency in light of the indirect consequences of sub-optimal 25(OH)D levels on long-term health (57). Insufficiency has been defined as serum 25(OH)D <50 nmol/L, with this higher threshold for clinical action more readily protecting patients against deficiency and associated risks of pathology, as well as somewhat accounting for the variable nature of vitamin D status in patients throughout the year (58) (59). The Institute of Medicine (IOM), based in the USA, has declared 50nmol/L as the 25(OH)D level which is sufficient for 97.5% of people; the Endocrine society went further, stating that deficiency is defined by 25(OH)D levels below 50nmol/L and

insufficiency between 52.5nmol/L and 72.5nmol/L (60) (21). As previously discussed, 25(OH)D is a stable molecule with a long serum biological half-life, making it a good biomarker and basis for a standardised measure of vitamin D status (22) (61). This measure increases uniformly in response to supplementation with both cholecalciferol and ergocalciferol (61) (62).

1.3.2 Prevalence of vitamin D deficiency in the UK

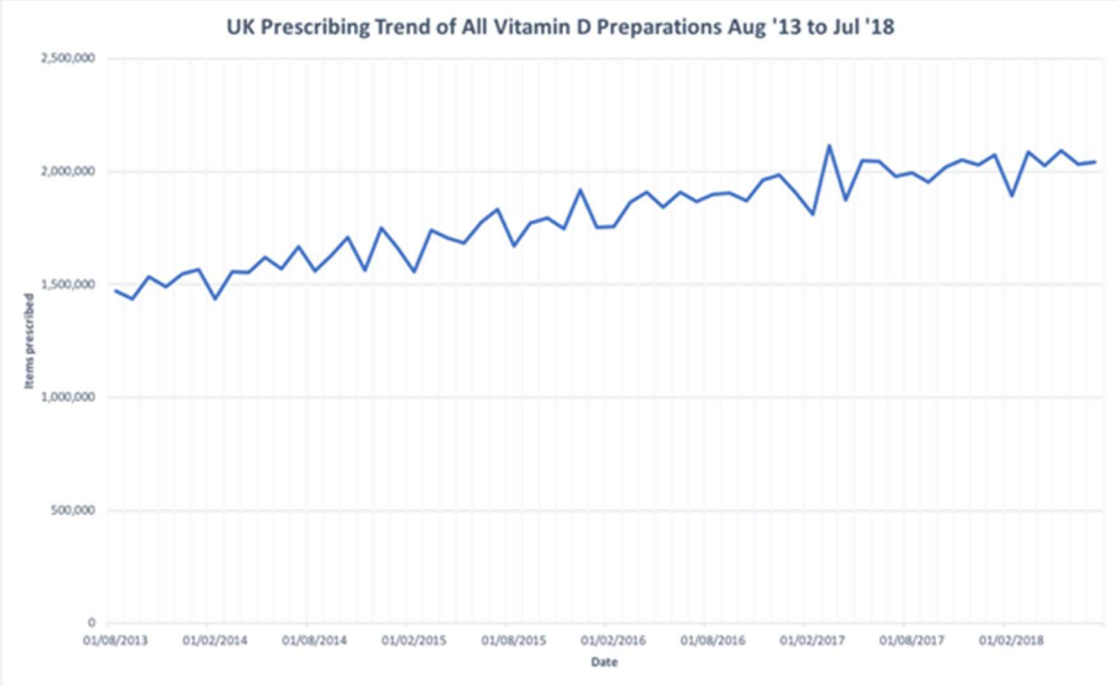

Figure 1.8- The UK prescribing trend for vitamin D products in the UK 2013-18 (66)

Between 2000 and 2014, there was a 15-fold increase in the diagnosis of vitamin D deficiency (63). In 2010 the UK Department of Health released guidelines recommending supplementation of all under-5s with vitamin D (64). The UK Chief Medical Officers in 2011-12 wrote messages to clinicians from a growing evidence base raising awareness of the increasing prevalence of vitamin D deficiency and rickets (65). Subsequently, this was followed by a steady increase in the prescription of vitamin D products in primary care

settings (Figure 1.8), approximately a 33% increase in 4.5 years (66). This change could potentially be augmented by an increase in testing frequency, due to the prevalence of sub-clinical vitamin D deficiency or insufficiency. The Royal College of Obstetricians and Gynaecologists (67) also encouraged the supplementation of all pregnant women in 2014 (67). The lack of a comprehensive supplementation programme in the UK has been linked to poor adherence (between 5%-20%) to vitamin D DRI guidelines in the 0-4 age group (68). This is despite schemes such as the UK government's 'Healthy Start' initiative, which gives patients receiving government benefits supplements. It has been criticised for its selective coverage, as there had been poor administration of the recommendations in the whole population (69).

1.4 Risk factors for vitamin D deficiency

There are a multitude of factors which contribute to vitamin D status; genetic, environmental and behavioural determinants may influence the risk of vitamin D deficiency (70).

1.4.1 Environmental determinants of vitamin D status

1.4.1.1 Ozone attenuation and the effect of latitude

There are several environmental factors which determine whether sufficient UVB radiation even reaches ground level before other factors can determine whether humans expose their skin for photosynthesis of previtamin D (28) (71) (72).

The stratospheric ozone (O_3) layer absorbs UVB radiation before it can travel on to Earth's surface; the energy provided by UVB radiation breaks O_3 molecules down into oxygen and

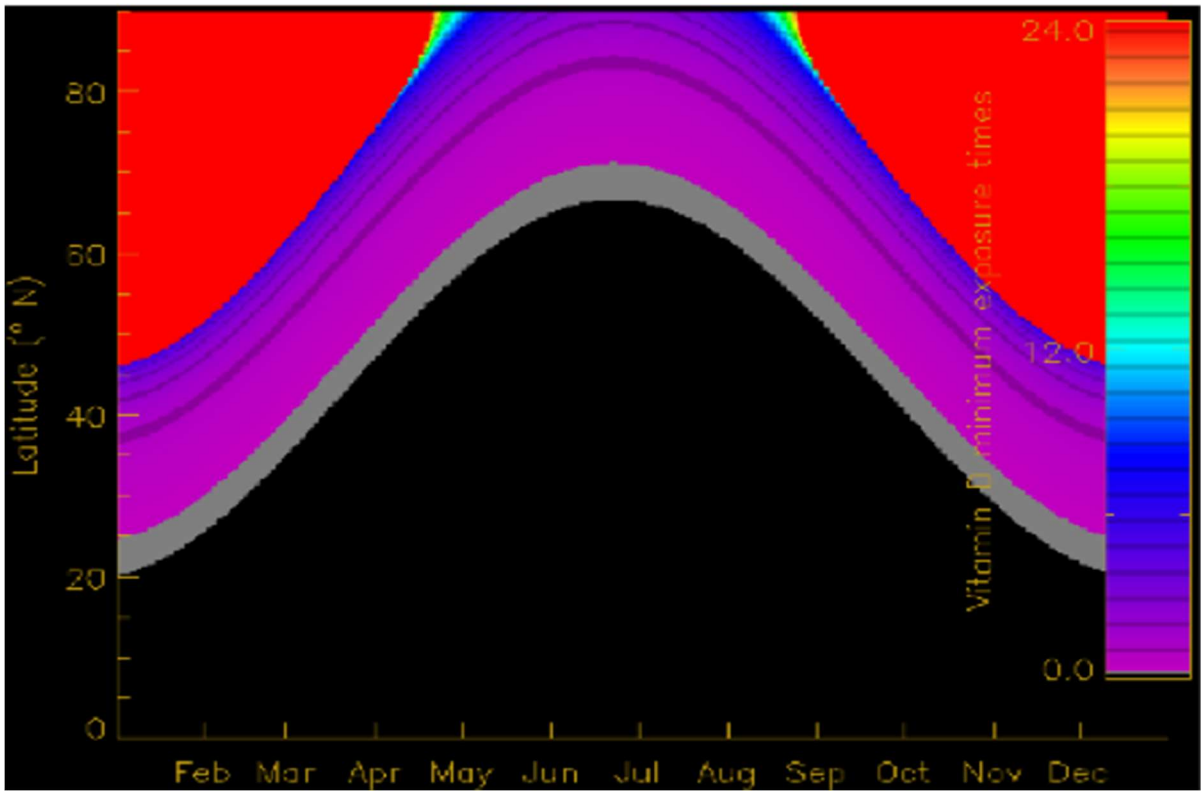

Figure 1.9- Thresholds for vitamin D synthesis at different months and latitudes.

Latitude-dependent, year-round representation on how long Caucasian patients need to spend outside on a clear day to synthesize the equivalent of 400 IU vitamin D. Black area shows when sufficient vitamin D can be obtained in minutes. (76)

the activation energy is supplied for the conversion reaction of 7-DHC to pre-vitamin D (73). The angle at which UVB radiation penetrates the stratosphere can consequently attenuates the resultant surface UVB levels. A more oblique angle will mean more O_3 atoms obstruct the solar UVB radiation on its path through the stratosphere (72) (74). This reaction releases free oxygen radicals, and in doing so releases thermal energy (72). This energy loss affects the intensity of the UVB reaching ground level, and therefore ultimately impacts the dose of UVB available to populations.

The solar zenith angle (SZA) represents the angle between the zenith, locally perpendicular to the Earth's surface, and the relative position of the sun (72). The SZA at any one location

is constantly changing, in the short term with the rotation of Earth on its axis and in the long term with the position of Earth as it orbits the Sun (73). Therefore, the time of day is important when determining optimum conditions for vitamin D synthesis, this effect is also heavily influenced by the time of year (Figure 1.9). The effect of seasonality in turn is mediated by latitude.

Locations of higher latitudes will have the impediment of a larger SZA, as the path through the ozone layer required for UVB radiation will be uniformly longer throughout the year than that at the equator (73) (75) (76). It has been shown that in the UK, the adult population has significantly lower 25(OH)D levels in the winter and spring than then rest of the year (77). Several studies have shown that SZA and factors that affect it such as seasonality and latitude is correlated with vitamin D status of the surface population. The 'vitamin D winter' period of the year, in which there is insufficient UVB intensity to produce pre-vitamin D in the skin, was found to be extended from November to February in Boston (with a latitude of 42.2°N) to October to March in Edmonton (52°N) (12). Another study showed that the 'vitamin D winter' lasted 8 months in Tromsø (69°N); and was non-existent in Crete (35°N) (73). Therefore, the challenge to people living further from the equator of obtaining adequate vitamin D is greater. This is because there is a smaller proportion of the year and the day in which they have the opportunity to go outside and expose themselves to UVB of sufficient intensity to catalyse the biological synthesis of cholecalciferol (Figure 1.9).

1.4.1.2 Other environmental sources of UVB attenuation

Another environmental determinant of surface UVB levels and vitamin D deficiency is cloud cover (76). Although the effect is variable, depending on cloud height or density, cloud cover

can be a potent contributing factor in UVB attenuation (76). Surface albedo (reflectivity) and altitude also impacts UVB levels; albedo can amplify UVB levels by reflecting solar radiation back up to clouds, which then reflect it back, and altitude raises UVB levels as radiation travels through less attenuating atmospheric molecules (76) . Pollution is another determinant of poor vitamin D synthesis and status; amongst other low-lying atmospheric pollutants, surface UVB radiation is attenuated by particulates produced by inefficient combustion of fossil fuels (72).

1.4.2 Genetic and behavioural risk factors

There are genetic variants which have been found to affect serum 25(OH)D levels. Variation of genes coding for the expression of CYP2R1, 7-DHC synthase, VDR and DBP has the potential to explain different vitamin D sensitivities within populations (70) (78) (79). Melanin expression is a major genetic determinant of vitamin D status in UVB-reliant populations. Produced by melanocytes in the epidermis, melanin absorbs energy from similar wavelengths of UVB radiation (295-320nm) to 7-DHC, leaving less available to catalyse the cutaneous conversion of 7-DHC to pre-vitamin D (71). As a result, patients with darker skin due to increased melanin concentrations require more UVB exposure to produce adequate circulating 25(OH)D levels and are at a significantly increased risk of severe deficiency, and prevalence of deficiency is indeed higher in these patients (61) (80) (63).

Maternal vitamin D deficiency is a strong predictor of neonatal deficiency as the fetus is entirely dependent on its mother for vitamin D, which affects normal growth, as well as skeletal and lung development during pregnancy (58) (67). Obesity significantly affects vitamin D status; adipose tissue can act as a vitamin D sink, making mobilisation of stores

difficult with large reservoirs of adipose in obese individuals leading to increased risk of deficiency (70) (81) (82). Increased adiposity is influenced by both genetic and environmental factors, and with a globally increasing prevalence of sedentary lifestyles, a decreased exposure to sunlight may be responsible for rising vitamin D deficiency in Western societies (70) (83).

Other pathology can lead to vitamin D deficiency. Malabsorption of fats impedes the acquisition of vitamin D through diet, therefore deficiency is a risk for patients with diseases, among others, such as coeliac disease, inflammatory bowel disease (IBD) and cystic fibrosis (CF) (59) (84). Patients with reduced mobility are less able to go outside independently and synthesize cholecalciferol, often leading to institutionalised elderly patients and younger patients with complex chronic health conditions becoming deficient without supplementation (28) (85) (56). Age itself is a risk factor for vitamin D deficiency, as keratinocytes in older skin produce lower concentrations of 7-DHC, raising the threshold of minimum sunlight exposure to achieve sufficient 25(OH)D levels for older individuals (76).

Behaviour impacts vitamin D status now more than ever. Adults and children in Western societies are spending less time outside, exposed to sunlight and concurrently adequate levels of UVB radiation (86) (87). Clothing also prevents UVB from reaching skin and covering a larger surface area of skin is a cultural practice more prevalent in different ethnic groups (80) (88). Sunscreen is widely used and is designed to block UVB rays from passing through the skin to prevent cellular and DNA damage, but it can theoretically limit the synthetic capacity of the skin to produce vitamin D (10) (89). It is, however, debatable whether this causes deficiency. Although it has been proven that proper application of sunscreen almost

completely inhibits the photo-conversion of 7-DHC, individuals do not necessarily apply sunscreen so scientifically (90) (91). Incomplete coverage and unintentional sun exposure may negate the efficient absorption of UVB radiation by sunscreen (76) (92).

Paradoxically, in countries in which seasonality plays little role in UVB exposure there is more sun-avoidance behaviour; this could be due to the heat of direct sunlight, skin cancer awareness campaigns, and the availability of modern, air-conditioned schools and childcare facilities (93).

1.4.3 Inadequacy of dietary sources

A factor contributing to vitamin D deficiency is the issue of the inadequacy of diet as a source of vitamin D to fall back on in the absence of UVB-mediated dermal production of vitamin D (94) (95) (96). Reported sources of dietary vitamin D such as fish, meat and dairy products, do not contain adequate vitamin D concentrations and are not consumed in enough quantities to maintain year-round sufficiency, hence the effect of changing seasons on vitamin D status in the UK (96) (97).

Otherwise proven to be an effective alternative course of action, there is no widespread fortification of food products with vitamin D in the UK, further exacerbating the issue of inadequate oral intake of vitamin D (13) (98) (99).

1.4.3.1 Oral intake of vitamin D in the UK

In 2016, the UK Scientific Advisory Committee on Nutrition (SACN) recommended a daily intake of 10 micrograms (400 IU) of vitamin D for all adults and children (100). The most

recent data from National Diet and Nutrition Survey (NDNS) conducted by Public Health England showed that between 2014/15 and 2015/6 only 21% of the daily recommended intake (DRI) of vitamin D was gleaned from dietary sources in 19-64 year-olds (101). Similarly, children aged between 18 months and 10 years only received 20% of their DRI from di*et al*one, and 65-74 year-olds received 35% (101). When adding vitamin D gained from any supplementation, children under 10 obtained a total of no more than 30% of their DRI, with 65-74 year-olds showing most improvement receiving 60% of their DRI from both diet and supplements (101).

The report illustrates firstly that the population, children under 10 years old especially, relies on sunlight far more heavily as a source for their vitamin D than diet. Secondly, the current level of increased supplementation in the UK, although to some extent improved intake, is inadequate to compensate from the lack of vitamin D intake from diet and dermal synthesis from solar UVB radiation (13) (56). Lastly, the report also shows that despite being the group with the lowest oral vitamin D intake, children aged 4-10 were found to have the lowest deficiency rates (10% had 25-hydroxyvitamin D levels <25nmol/L), whereas the 11-18 age group had the highest (26% were deficient) (101). Clearly the children aged 4-10 years old utilised UVB as a source for vitamin D far better than other age groups, perhaps because of differences in sun-seeking behaviour (102) (103). These statistics are in the context of defining vitamin D deficiency as 25(OH)D <25nmol/L, ignoring the widely discussed notion that other non-skeletal pathologies can manifest at levels above this cut-off (104).

1.5 Skeletal effects of vitamin D deficiency

The impact of vitamin D deficiency on the skeletal system has been experienced by children throughout the ages, and now once again at an increasing prevalence in the UK through the pathology of rickets (105). Rickets is a condition synonymous with vitamin D deficiency and is often its most obvious marker of severe deficiency (84). Growing children are affected by rickets due to the failure of mineralisation of the area of new bone formation by endochondral ossification, located in growth plates at bone metaphyses (106). This is caused by an environment of chronic low calcium or phosphate ion concentrations in the extracellular fluid (ECF) in osteoid tissue (106).

Vitamin D deficiency can affect bones in this way, as 1,25-dihydroxyvitamin D upregulates the TRPV5 Ca^{2+} channel in enterocytes, enabling efficient calcium absorption and maintenance of adequate blood concentrations (27). Interestingly, it is hypophosphataemia that induces an impairment of chondrocyte apoptosis; PTH is released in response to hypocalcaemia, which in turn causes collateral renal phosphate excretion (106). Vitamin D supplementation has been found to treat rickets patients and prophylaxis prevents the manifestation of calcipaenic rickets (68).

Regarding children born of vitamin D deficient mothers there is no proven increase in rickets incidence (107). Although a recent Randomised Controlled Trial (RCT) has shown no benefit of maternal supplementation to bone mineral content of their 2-week old children, vitamin D supplementation has previously been shown to benefit long-term bone mineral density (108). Maternal vitamin D deficiency during pregnancy has been found to be a particularly significant determinant in the growth and bone mass in children until they are 9 years old

(109). Children are likely to share the genetic and environmental risk factors as their parents; however, it has been found that supplementation of breastfeeding infants with vitamin D negates this long-term effect on bone mineral density (110).

Another manifestation of severe vitamin D deficiency is hypocalcaemia, complications of which include seizures and dilated cardiomyopathy (68) (111). The incidence of hypocalcaemic seizures is 3.49 per million children aged 0-15 years, with a large proportion of those children affected in at-risk groups of vitamin D deficiency. For example, those with increased skin melanin concentrations in people of Black and South Asian ethnicities in the UK are at greater risk of such severe complications of deficiency (112). Hypocalcaemic seizures and associated cardiomyopathy pose a serious threat to the at-risk patient population, these pathologies are deadly marker conditions which highlight the necessity of population vitamin D supplementation and fortification (105).

1.6 Extra-skeletal effects of vitamin D deficiency

Further to its conventional effects on bone homeostasis, vitamin D and its deficiency has been found to have numerous extraskeletal effects (104). As previously discussed in Section 1.2.3, immune cells are particularly sensitive to changes in concentration of 25-hydroxyvitamin D due to their expression of 1-alpha hydroxylase enzyme. By this mechanism, vitamin D selectively increased immune defences and shifts phenotypes of immune cells to favour regulation rather than inflammation (27) (49).

1.6.1 Vitamin D and respiratory infections

Vitamin D has shown to enhance innate immunity: macrophages activate and eliminate intracellular *Mycobacterium tuberculosis* more effectively in response to activated vitamin D driven by upregulation of autophagy and cathelicidin production, aiding resolution of the disease (113) (114). Antimicrobial peptides that $1,25(OH)_2D$ encourages the production of such as β-defensins and cathelicidins also strengthens the innate immune response to respiratory viruses (42). In accordance with these physiological effects, vitamin D deficiency has been shown to increase lower respiratory tract infection (LRTI) rates in neonates and children (115) (116) (117). A recent individual participant data meta-analysis of randomised controlled trials evaluated whether supplementation with vitamin D reduces LRTI risk and found it to be safe and providing an overall protective effect against infection (118). This was most marked in patients that were already vitamin D-deficient (118). Supplementation with vitamin D has also been shown to reduce infective exacerbation rates of chronic obstructive pulmonary disease (COPD) patients, with the enhanced activity of the innate immune system postulated to be the cause of this protective antiviral effect (119). This marked bolstering of the innate immune system by vitamin D is indicative of the potential of how the immune-specific processes driven by this secosteroid hormone could be harnessed for the benefit of patients in clinical practice and the general population.

1.6.2 Vitamin D and asthma

Asthma is another respiratory condition heavily influenced by the activities of immune cells and has been identified as a condition which vitamin D supplementation could target (120) (121). Affecting over 330 million adults and children worldwide, asthma is a chronic inflammatory disease of the respiratory system, diagnosed clinically and characterised by

reversibility of bronchoconstriction upon administration of β_2 agonists (122) (123). Innate and adaptive immune cells mediate inflammation and hyper-responsivity to stimuli, goblet cell hyperplasia leading to excessive mucus production, oedema and airway remodelling (123). Long-term maintenance of these inflammatory processes is driven by lymphocytes such as Th2 and Th17 cells, polarised by dendritic cells releasing cytokines such as IL-4, IL-5 and IL-17 (123). Environmental factors that can precipitate and perpetuate asthma include cigarette smoke, poor air quality due to pollution and viral infections (124). There is heavy interplay between predisposing genes of atopy which increase the risk of disease manifestation and progression, and the environmental exposures which mediate their expression (125).

A major source of mortality in asthma patients is asthma exacerbations, commonly caused by viral LRTIs (126) (127). Vitamin D deficiency has been associated with a marked reduction in lung function and an increase in asthma severity; UK adults with inhaled corticosteroid (ICS) controlled asthma see a marked increase in vitamin D insufficiency relative to the general population (128) (129). With immunomodulatory actions of vitamin D being discovered, such as an enhanced innate anti-viral mucosal defence and the promotion of a regulatory adaptive immune environment, it is perhaps unsurprising that vitamin D deficiency leads to worse asthma control and supplementation leads to fewer exacerbations (130) (127) (131). It has also been proposed that vitamin D's effects on cell cycle regulation can ameliorate the long-term damaging effects of airway remodelling in response to chronic inflammation (132). Patients treated by ICS are at risk of impaired growth when treated with higher doses, and vitamin D has been shown to enhance the response of the airways to ICS

treatment (121). This shows potential for vitamin D supplementation to complement asthma treatment regimens, subjecting patients to less intensive treatment.

1.6.3 Vitamin D and other chronic diseases

Autoimmune diseases such as type 1 diabetes mellitus, systemic lupus erythematosus (SLE), multiple sclerosis (MS) and inflammatory bowel disease (IBD) have been shown to correlate with vitamin D deficiency, a representation of the robust effects on the adaptive immune system of vitamin D (38) (133) (134) (135).

There has been much interest in investigating the potential effects of vitamin D deficiency on cancer rates and the benefits of supplementation (33). It is hypothesized that 7-DHC and its conversion to vitamin D has its evolutionary beginnings as a natural protection of DNA from harmful UVB rays, allowing organisms to thrive in direct sunlight (21). Despite the damaging effects of UVB radiation on DNA leading to an increased risk of skin cancer following prolonged exposure, 1,25-dihydroxyvitamin D has been shown to have regulatory effects on the cell cycle and apoptosis during in vitro studies (136).

Proposed mechanisms include upregulation of the p53, p21 and p27 proteins, which halt the cell cycle at key checkpoints, notably between G1 and S phases (25) (137). While there is observational evidence of increased vitamin D insufficiency rates in cancer patients and a latitudinal effect on the prevalence of some cancers, recent RCTs and systematic reviews of meta-analyses have shown no effect of vitamin D supplementation on cancer rates (30) (138).

1.6.4 Vitamin D and maternal health

In addition to improvements to long-term child bone density, vitamin D supplementation during pregnancy has been shown to have beneficial effects on neonatal birthweight, as well as reducing the risk of maternal pre-eclampsia and pre-term birth (139). Suggested mechanisms include the importance of 1,25-dihydroxyvitamin D to early placental development (140). Extrarenal 1α-hydroxylase distribution analyses have found the conversion enzyme to be present in both endometrial tissue and foetal trophoblast, exhibiting the role of active vitamin D as a potential immunomodulator in the mediation of blastocyst implantation, acting to prevent rejection (37).

Pre-eclampsia is an obstetric condition caused by the ineffective infiltration of the foetal trophoblast into the endometrial decidua; it has a high mortality rate, its risks including placental abruption, neurological and cardiovascular complications, low birth weight and pre-term birth (141). A recent meta-analysis studying the relationship between pre-eclampsia rates and vitamin D insufficiency gave an odds ratio of 1.79 (95% Cis 1.25-2.58) (140). Despite some conflicting studies reporting no benefit of supplementation, the Royal College of Obstetricians and Gynaecologists recommend the supplementation of all pregnant women with vitamin D (142) (67).

1.7 Summary

This chapter has explored the extensive physiology of vitamin D and the clinical implications of deficiency. Vitamin D status has been discussed as an important aspect of health that is very sensitive to environmental changes. The different environmental determinants of

efficient endogenous vitamin D synthesis in populations have been outlined, as have other genetic and behavioural factors which impact vitamin D status on the level of the individual.

The next chapter will focus on the relationships between paediatric asthma admissions and several environmental factors on a regional level. The epidemiology and pathophysiology of asthma will be covered in greater depth, as will the previously observed effects and theoretical mechanisms of vitamin D on the condition. A confirmatory analysis of a study this research group carried out will be performed, investigating the effects of meteorological factors and acute asthma admissions in English children (143).

2 The impact of weather on asthma

2.1 Introduction

A belief that weather can affect health is as old as medicine itself. In the 5th century BC, Hippocrates described in great detail his understanding of how latitude, seasonality, wind temperature and rainfall affects the health of a population in his treatise 'On Air, Waters and Places' (144). 2500 years later, we might have a better understanding of exactly how and what meteorological factors might affect population health than the Greeks did, but Hippocrates may not have been entirely wrong in saying that "with the seasons the digestive organs of men undergo a change". But just how much does meteorology, the study of 'high up things' and 'celestial phenomena' affect health? Despite the long-held beliefs that weather interacts with human health, proving a causal link has been difficult.

In 2017, Davies *et al*. gave an insight as to how weather might affect children with asthma in the UK (143). In many ways these observations were the starting point for this thesis which aims to confirm their observations and refine the analyses undertaken. They reported that there is a significant reduction in asthma admissions in regions receiving more annual hours of sunlight, controlling for socioeconomic deprivation (143). One limitation of their analysis was a failure to consider other correlated weather indices of temperature and rainfall. In this chapter a confirmatory analysis of the same dataset using a similar methodology will be performed, exploring the additional effects of different weather variables on asthma from a regional perspective as well as examining the impact of the socioeconomic deprivation, as a covariate, on any observed association. Before this, asthma as a condition will be briefly

outlined and the mechanisms by which weather could potentially impact admissions rates through vitamin D status will be summarised.

2.2 Background

2.2.1 Asthma is common and important

Asthma is a common respiratory disease among children; the UK has some of the highest asthma prevalence rates in the world, with 1.1 million children currently receiving treatment (145). Children aged 0-14 are by far the largest age group of the 75,000 patients who are admitted to UK emergency departments due to asthma (146). These exacerbations are distressing and potentially life-threatening.

Asthma is a complex genetic condition, and manifests phenotypically with highly variable severity. Asthma is a T-helper-2 (T_H2) mediated chronic immunological condition affecting the respiratory immune system (147). Its features include bronchiolar hyperresponsivity, excess mucus secretion and eventual airway remodelling (148). Family history of asthma or allergy, as well as poor early lung development, predisposes children to developing asthma (149).

While a myriad of heterogenous genetic factors can determine the presence and severity of the disease, precipitation of the clinical phenotype is also determined by environmental factors such as allergens and respiratory viruses (150). While viruses and allergens can cause bronchospasm, asthma exacerbations can also be triggered by exercise, air pollutants (including tobacco smoke), occupational environmental exposure, emotional distress and certain medications (151). The symptoms of asthma caused by airflow obstruction, such as

cough, wheezing, sleep disturbance, dyspnoea and poor exercise tolerance, can, in most patients, be relieved by β-adrenergic bronchodilators and prevented by inhaled corticosteroid (ICS) treatment (152). Severe phenotypes receive more intensive care along the asthma treatment pathway; disease severity and adherence to medical management of the condition are major factors in determining the risk of acute asthma exacerbations (153).

2.2.2 Environmental influence on asthma through vitamin D

Given its pleiotropic effects, Vitamin D has a significant potential to interact with the immunological regulation of asthma, in addition to having significant interplay between environmental factors which modulate the disease (149). The influence vitamin D has on the polarisation of T-cell phenotypes is amplified throughout the immune system; it drives the shift towards anti-inflammatory iTreg cell activity to tip the balance against the T_H2 and T_H17 cell phenotypes which perpetuate the chronic inflammatory tissue environment in asthma which preventer medication suppresses (52).

Vitamin D supplementation has been shown to reduce asthma admissions in patients on ICS treatment (127). Likewise, vitamin D deficient adults and children have a greater susceptibility to exacerbation (154) (129). Increased anti-viral activity of respiratory epithelial cells and leukocytes also reduce the risk of severe asthma by diminishing the effect of one of its determinants: respiratory viruses (42).

2.2.3 Other environmental determinants of asthma

Vitamin D deficiency and asthma share the common risk factor of air pollution. In addition to contributing towards asthma pathogenesis, airborne pollutants also absorb UVB radiation

before it can be utilised by individuals to synthesize vitamin D (155) (156). Measures of pollution such as nitrogen dioxide (NO_2) and particulate matter ($PM_{2.5}$, PM_{10}) have been found to be raised in areas where childhood asthma is more prevalent and severe (157). Vitamin D-independent effects of sunlight on asthma control have also been reported, asthma control has been anecdotally seen to improve upon arrival in warmer climates at lower latitudes when vitamin D status has not had time to improve.

Figure 2.1- Map of climate districts used to calculate climate data averages in England and Wales (259).

Weather and seasonality affect asthma in other ways. Acute asthma admissions have been seen to rise during thunderstorms, due to changes in air dust particle and ozone gas concentrations, as well as during periods of high pollen exposure (156) (158). Respiratory viruses, a risk factor for acute asthma admission, have found to be more common during winter with higher infection rates (159). Asthma prevalence in children has been positively correlated with rainfall (160). There are other methods by which weather can affect vitamin D status. For example, behavioural studies have shown individuals who spend more time indoors have lower 25(OH)D levels than those who do not (86). Rainfall and temperature affect human behaviour; if people in a region spend time indoors and cover up more during cold or rainy months they have less of an opportunity to expose themselves to UVB radiation and acquire adequate vitamin D (161).

2.3 Methods

In this confirmatory analysis, the published methodology undertaken by Davies *et al* in 2017 is closely followed, using the same data sources for meteorological and admissions data (143). Meteorological data were collected from the online open access Met Office climate summaries (162). The annual hours of sunshine data were from 6 regions from England and Wales: East Anglia; England East & Northeast; the Midlands; England Northwest & North Wales; England Southeast & Central; and England Southwest & South Wales (Figure 2.1). The Met Office has a national network of weather stations. Using photodiode sensors, these stations detect solar energy with a threshold of 120 Watts/m^2 and record how many hours it is exposed to sunlight (Figure 2.2) (163). Total annual rainfall and average annual temperature were included as covariates in this analysis, again using the public Met Office meteorological data (162). Synoptic meteorological data are assimilated from the weather stations in each region, and regional values are generated for each month, season and year.

The synoptic meteorological data provided regional annual recordings starting from March each year, and the data were manipulated such that the data described the weather recordings starting from April each year. In the case of the total hours of sunshine and total rainfall variables, for each region the March recordings were subtracted from the annual total, then the March recordings from the subsequent year were added to give an April to March total (162). Since the temperature data were an annual average for each region, the average temperature was multiplied by 12, the March temperature recording from that year was subtracted, the subsequent year's March temperature added, then this result was divided by 12 to give the annual April to March average temperature.

These corrections to the data were made in order to match the time period measured to the Hospital Episodes Statistics (HES) admissions data starting from April 1st each year. The HES database is compiled by the National Health Service (NHS), and records patient admissions to emergency departments in English NHS hospitals (164). HES data describing admissions with acute asthma exacerbations for 9 years from 2002/3 to 2010/11 was used, including the International Classification of Disease (ICD)-10 codes J45 (asthma) and J46 (status asthmaticus) (165). These data gave indirectly age-gender standardised rates for asthma admissions per 100,000 per annum in children under 16 years old. Rates in the dataset are given at the level of government office region, strategic health authority (SHA), local authority (LA), and Primary Care Trust (PCT) (boundaries as of 2011). The 150 Primary Care Trusts were mapped onto the 6 Met Office regions (Figure 2.1) and average admission rates per 100,000 per annum were calculated accordingly. For the socioeconomic deprivation covariate included in the model, 2007 Income Deprivation Affecting Children Index (IDACI) scores were found for each corresponding region.

Figure 2.2- Sunshine duration meter used by many automated Met Office weather stations (162)

Statistical analysis was carried out using multivariable linear regression, following the Davies *et al* 2017 method (143). Included in the model for the preliminary analysis were variables representing the regional age-gender corrected hospital admission rates for asthma, total annual hours of sunshine (HoS), total annual rainfall, average temperature, and IDACI scores.

Statistical analysis was carried out by using STATA software version 8.0 (STATA Corp, Texas, USA).

2.4 Results

The descriptive statistics for these data are congruent with those detailed in Davies *et al* 2017 (143). The number of children under 16 who were admitted to emergency departments with acute asthma exacerbations in England between 2002/3 and 2010/11 was 220,913. The year with the lowest overall number of admissions nationally was 2007/8, with 22,751 children being admitted with asthma. In the previous year, 26,979 children were admitted with asthma, the highest number of admissions nationally in the period of this study. The estimated child population of this study fluctuated within the range of 9,654,027 in 2007/8 and 9,853,580 in 2002/3.

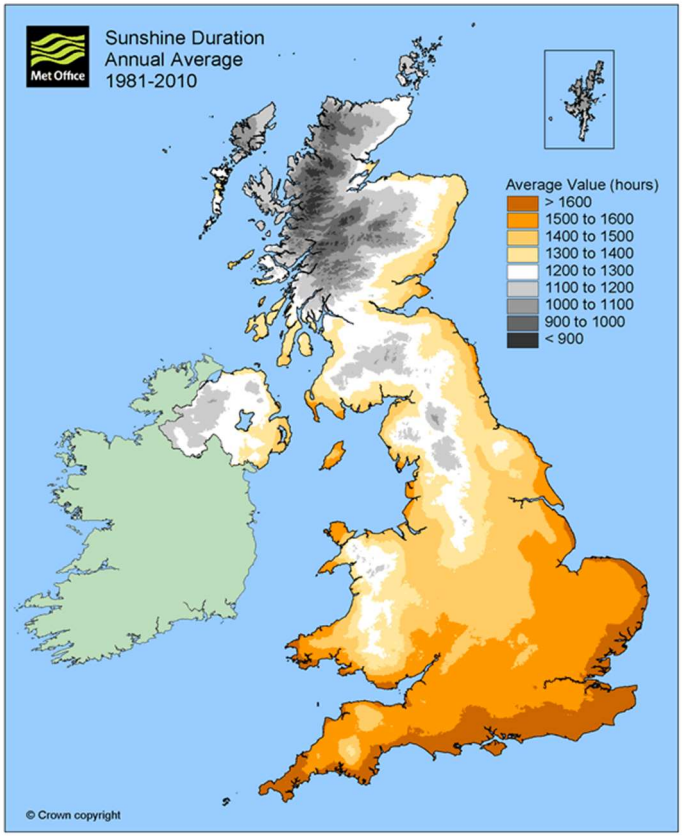

Figure 2.3- Map of UK annual hours of sunshine 1981-2010

Regional indirectly age-gender standardised asthma admission rates per 100,000 children under 16 per annum were calculated from matched PCT averages. The mean asthma admission rate over all years and regions was 265.3 per 100,000 per annum, and the median was 258.4 per 100,000 per annum.

The region with the lowest admission rate was England Southwest & South Wales in 2010/11 with a rate of 177.4 per 100,000 per annum, whereas the PCT with the lowest admissions rate was Tower Hamlets PCT in 2006/7 with a rate of 16.10 per 100,000 per annum. The highest regional admissions rate was 428.74 per 100,000 per annum, in the England Northwest & North Wales region in 2006/7; the highest PCT admissions rate was 872.83 per 100,000 per annum, in the Liverpool PCT in 2006/7. Indeed, 5 of the 10 highest PCT admission rates (calculated for each year separately) in the 9-year period were found in the Liverpool PCT.

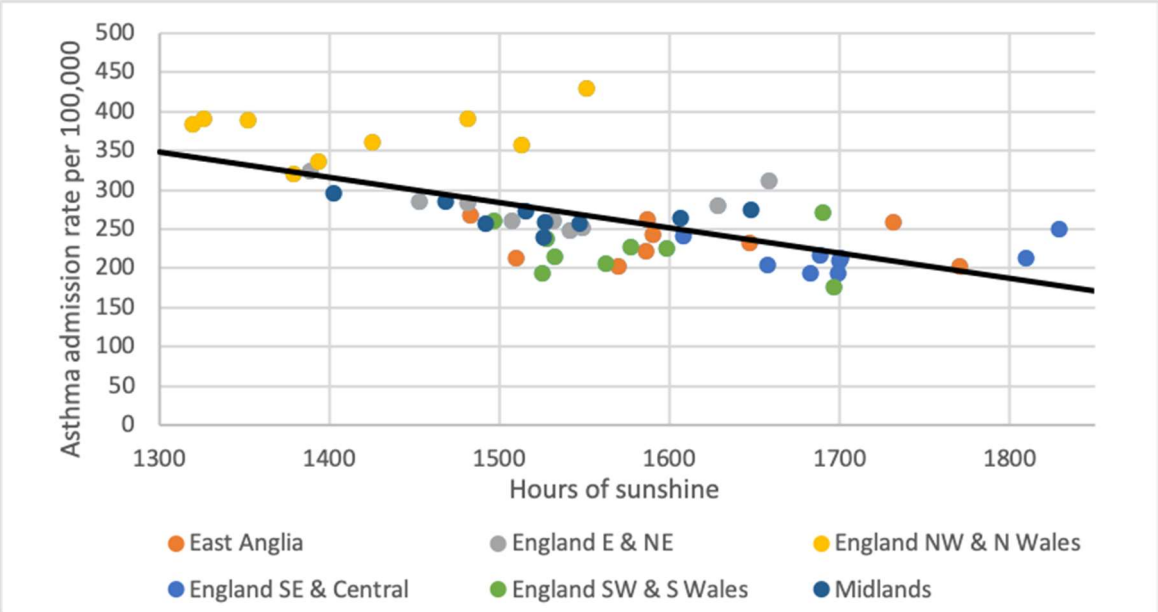

Figure 2.4- Scatter graph showing asthma admission rates and hours of sunshine in 6 Met Office regions

The mean hours of sunshine for all years and region was 1560.8, and the median was 1548.2. The Met Office region receiving the least annual hours of sunshine was England Northwest & North Wales, giving the lowest value of 1320 hours of sunshine in 2004/5, while the region with the most hours of sunshine was England Southeast & Central in 2006/7. These findings are in accordance with historical hours of sunshine data for the country (Figure 2.3).

As Figure 2.4 shows, on average asthma admissions rate for each region is seen to increase when the area is exposed to fewer hours of sunshine. Linear regression was used to analyse this relationship; in addition to asthma admission rate and HoS, rainfall, temperature, latitude, longitude and IDACI score were included as covariates in this model.

Table 2.1- Univariate linear regression analysis of the association between asthma admission rates per 100,000 per annum and hours of sunshine

	Asthma admission rate per 100,000 per annum			
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**
Hours of sunshine	-0.322	-0.429, -0.214	<0.001	-6.01

Adjusted R^2 (variance) = 0.398

Table 2.2- Analysis of the association between asthma admissions and meteorological factors using a linear regression model.

	Asthma admission rate per 100,000 per annum			
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**
Hours of sunshine	-0.247	-0.392, -0.102	<0.001	-3.43
Rainfall	0.0267	-0.0246, 0.0780	0.301	1.05
Temperature	-11.0	-33.5, 11.5	0.330	-0.98
IDACI score	4.29	1.03, 7.55	<0.001	2.65

Adjusted R^2 (variance) = 0.474

As shown in Table 2.2, while hours of sunshine and socioeconomic deprivation significantly affect asthma admission rates, rainfall and temperature had no significant interaction with asthma admissions. According to this model, every additional 100 hours of sunlight is associated with a reduction in regional asthma admission rates in children by 24.7 per 100,000 per annum, which is 9.31% of the mean value. Every increase in IDACI score by 0.1 is associated with a 4.29 per 100,000 per annum increase in asthma admission rates, a 9.31% increase relative to the mean value. The adjusted R^2 (variance) value generated in this analysis is 0.474. One interpretation of this is that the model here estimates that almost half of the variation in asthma admissions can be explained by variables included.

Further analysis was carried out using an extended generalised estimating equation (GEE), as this test is useful for estimating generalised linear models fits models which use longitudinal panel data such as is used in this study into factors affecting asthma admissions over time (166). This was done as a 'second check' of the data and modelling.

Table 2.3- Results from extended generalised estimating equation, showing the associations between asthma admissions and meteorological factors.

	Asthma admission rate per 100,000 per annum			
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**z statistic**
Hours of sunshine	-0.391	-0.533, -0.248	<0.001	-5.38
Rainfall	0.0127	-0.0206, 0.0460	0.453	0.75
Temperature	-12.5	-38.3, 13.2	0.341	-0.95
IDACI score	4.19	2.06, 6.31	<0.001	3.86

Wald $chi^2(5)=175.62$, Scale parameter=1886.672

As shown in Table 2.3, this analysis produces remarkably consistent results with the originally described methodology. Table 2 shows both HoS and IDACI scores remained a significant determinant of asthma admission rates in children, unlike rainfall and temperature variables. The regression coefficient for HoS increases by over 50% in this extended GEE compared to that in the linear regression (Table 2.2), showing every additional 100 HoS is associated with a reduction in asthma admission rates by 39.1 per 100,000 per annum. The Wald chi^2 test gave a result of 175.62 with 5 degrees of freedom, which implies that the variable associations found in this model contribute to the regional changes in acute paediatric asthma admissions. The scale parameter value of approximately 1887 shows that there is a wide distribution of these data.

2.5 Discussion

This analysis confirms the validity of the findings of Davies *et al*. 2017; the results of the linear regression carried out in this chapter, using the same data sources to generate variables, matched the findings of the original paper (143). The effect of regional sunlight exposure on reducing asthma admissions rates found by Davies *et al*. and reproduced here is strong supporting evidence with strengthens the argument that the climate in which we live in can impact disease profiles on an epidemiological scale.

Of the climatological variables included in the linear regression model, only total annual hours of sunshine was found to significantly impact admission rates; rainfall and temperature were found to have no significant effect. This effect is seen to increase in magnitude when applying an extended GEE. An explanation for this is that the relationship found is not linear, and unlike the initial regression analysis, the extended GEE does not rely upon the assumption of linearity. Vitamin D status is a biologically plausible link between greater sunlight exposure and changes in asthma control or phenotype seen on an epidemiological level (154) (129). While sunlight duration does not take into account surface UVB intensity, known to be the most accurate predictor of vitamin D synthesis efficiency, it serves as a useful indirect marker of vitamin D status on a population level (167).

When individual years were analysed in isolation, not one of the individual year analyses carried out showed a significant association between HoS and asthma admission rates and only 2002 and 2010 saw significant relationships both between IDACI and asthma admission rates. The reason behind this loss of effect detection is probably because each year provided only 6 data points for the model to use. Despite the large regional populations, the year-on-

year effect would potentially be better examined at a different level of granularity, for example at PCT level. Regrettably, there was no time to find weather station data for the 150 individual PCTs, but analysis at this level might be a better way to observe the factors at play in this model.

Reassuringly, socioeconomic deprivation was a potentially confounding covariate in the regression model and moreover it did not render the effect of HoS insignificant. A crude univariate linear regression showed deprivation to be significantly associated with asthma admission rates ($p=0.033$), while deprivation has no significant relationship independently with HoS in this model ($p=0.983$). This would imply that IDACI does not confound the relationship between HoS and asthma admission rates. The inverse care law states that healthcare is less accessible in areas of greater need and associated socioeconomic deprivation (168). In both urban and rural areas, it is primary care services in deprived areas that are more vulnerable to a lack of resources to treat their populations (169). The large majority of children with asthma are managed in primary care, and when compounded by other factors that are liked to deprivation that affect asthma control such as smoking, this could explain the link between deprivation and asthma admission rates seen in these analyses.

The effects seen in this study are stronger than those seen in large international studies (160). England is a particularly appropriate country in which this ecological study on the impact of vitamin D on child health was carried out. There is a largely unsupplemented population with very little vitamin D food fortification. Sunlight duration and UVB levels are subject to much geographical and seasonal variation. With different factors which could

potentially mask the efforts of the skin to synthesize endogenous vitamin D removed, varying environmental factors serve as a better indirect marker for vitamin D status on a population level. Indeed, using this proxy method requires less effort, allows larger populations to be studied and protects patient anonymity more than measuring individuals' serum 25(OH)D levels.

2.5.1 Strengths and limitations

The asthma admission rates provided by the HES data were generated from large populations. Being able to manipulate the data from the PCT level made matching to the 6 Met Office regions very accurate; the alignment of the regional populations that the asthma and climate variables were derived from strengthened the model. However, there is a limitation in that this matching process was not complete. Two of the six Met Office regions included parts of Wales (England Northwest & North Wales and England Southwest & South Wales), meaning that Welsh meteorological data were analysed alongside admissions data taken from English regions. This lack of corresponding asthma admission rates in Welsh children could be a potential source of error, although the Met Office grouped regions due to the relative uniformity (particularly between North Wales and Northwest England) of the local climate recordings (see Figure 2.3). However, when matching could be made as close as possible, this was done.

The modification of the annual weather data so that the year started describing meteorological variable in April rather than March allowed further alignment to the HES data, ensuring the populations both sets of variables were as similar as possible. Another limitation of the data was that only 6 separate geographical regions were examined. While

the Met Office generates synoptic weather data from its national network of weather stations, there is a loss of detail at different local geographical regions when condensing the recordings to give results for six large regions. As stated above, it might have been a more appropriate level of analysis if climate data were obtained for PCT regions to analyse the environmental determinants of asthma admission rates at a more granular aggregate level, rather than matching admissions data to 6 Met Office synoptic climate regions.

The nature of using hospital admissions data is such that it may underestimate the prevalence or symptom control of asthma due to different asthma management in rural areas. Individuals living in rural areas have less access to healthcare than those living in urban areas (170). Only patients presenting to hospitals, admitted with ICD-10 code J45 asthma and J46 status asthmaticus, were recorded in the HES database and contributed to the PCT then regional admissions rates. If asthma patients in rural settings are better managed in primary care and do not present to hospital the admission rates used in the analyses will be underestimated throughout this thesis. Differences in primary care management of asthma, as well as environmental differences in rural areas such as lower aerosol pollution, may reduce the risk of developing asthma and being coded as an admission in secondary care hospitals. The degree to which rural primary care asthma management, which may affect the generalisability of our findings, is not corrected for in our analyses, but rurality could be controlled for when continuing this research at a more granular level.

As Davies *et al* point out in the discussion of their original paper, children with more severe asthma could avoid outdoor activity and therefore become more likely to be deficient in

vitamin D, rather than vitamin D impacting the disease on a physiological level. The potential solution to this problem that they gave could also apply to this confirmatory analysis: due to such a large population being included in this model, the potential confounder would be controlled for as the regional weather data used in this analysis determines the ability of the whole child population of England to synthesize sufficient vitamin D to prevent clinical pathology (143).

The HES data coding and extraction method has in the past been criticised for being inconsistent and inefficient, relying on good clinical recording in scanned patient notes. However, evidence from quality reviewing in 2011 suggests that in the decade of the study period, the accuracy of HES data improved significantly and is suitable for research and managerial decision-making (171). A potential weakness of HES data in the context of this analysis is that repeat admissions are not recorded, meaning very poorly controlled children with more severe asthma phenotypes could cause overestimation of population asthma admission rates.

A strength of this study is its nationwide scope: the average child population in England in the study period (2002/3-2010/11) from the HES data was 9,731,440. This scale is necessary when examining the effects of long-term weather patterns on population health. By using annualised meteorological data, the effect of seasonality, an effect that is particularly strong in the UK, on vitamin D status and the pathologies affected by deficiency is controlled for. A possible focus for future research would be examining the association between asthma admission rates and hours of sunshine in different seasons and both patient 25(OH)D levels and asthma admission rates.

2.5.2 Implications for clinical practice

As is the case with the original Davies *et al* 2017 paper, the results found in this confirmatory analysis supports the growing body of evidence that vitamin D deficiency pervasively affects extra-skeletal health. In later chapters the effects of factors more profoundly affecting vitamin D status, such as sunlight and UVB radiation levels, on other diseases will be explored, but this set of analyses should affect the practice of clinicians managing asthma in children in particular.

As stated above, for every 100 hours of sunlight a region receives, its overall asthma admission rate is reduced by 24.7 per 100,000 per annum which equates to an approximate reduction of asthma admissions for children of 10%. Given the huge cost of asthma on UK health expenditure this is an important observation. This research demonstrates how sunlight exposure and taking vitamin D supplements could relate to better health outcomes for children on a population level.

There are pertinent messages to be taken from these results by public health clinicians. Recent public health campaigns have advised sun avoidance and comprehensive application of sun screen (89). Judicious application of sun screen is prudent to avoid erythema during long periods of sun exposure; however, it may be unnecessary for shorter periods of outdoor activity. As outlined by Webb in 2006, there is a limit to the quantity of pre-vitamin D that can be synthesized in the skin in a certain time, therefore there is little benefit in prolonged unprotected exposure (76). She goes on to support this by stating that pre-vitamin D_3 breaks down into inert isomers more, following prolonged UVB exposure, as does

vitamin D_3. Short, regular, unprotected periods of sunlight exposure should therefore provide adequate opportunity to synthesize sufficient levels of vitamin D.

Further to this, those treating asthma in children should bear in mind the heightened challenge to patients controlling their condition if they live in a less sunny region (see Figure 2.3) or if they are especially vulnerable to vitamin D deficiency. For example, if they have dark skin or cannot go outdoors. Taking these factors into account when managing exacerbation risk in such vulnerable children with chronic asthma could improve their outcomes

2.6 Summary

In this chapter, the results of the analysis of the association between asthma and hours of sunshine by Davies *et al* were accurately reproduced. The pathology of asthma and the theoretical targets in the disease process which vitamin D can ameliorate have been explored, in addition to other mechanisms by which environmental factors can affect asthma. While rainfall and temperature did not affect asthma admission rates in English children, hours of sunshine proved to be a significant and powerful determinant of acute paediatric asthma exacerbations. Deprivation has complex and wide-ranging interactions with asthma but did not remove hours of sunshine from significance in this model.

The next chapters will follow a similar methodology to the analyses carried out in this one, focusing instead on entirely novel analyses paediatric lower respiratory tract infection (LRTI) and gastroenteritis admission rates. Asthma is a chronic, complex genetic condition exacerbated by many factors including acute viral infections. In contrast, LRTIs and

gastroenteritis trigger non-specific, anti-viral responses which vitamin D can enhance. The epidemiology and pathology of LRTI and gastroenteritis will be explored, as will several proposed mechanisms by which environmental factors could affect admission rates. While an appropriate shift in focus as this thesis progresses, potential interactions between environmental factors with this different disease of the respiratory system could therefore provide another insight into the effect of vitamin D status and child population health.

3 The impact of weather on lower respiratory tract infections

3.1 Introduction

The gas exchange surface in adult human lungs is approximately 140m^2. This makes the lungs the organ with the largest surface area in the human body (172). Digestive gut mucosa and the skin have surface areas of around 32m^2 and between 2 and 25m^2 respectively (173) (174). All three have contact with the outside environment, and therefore have mechanisms to function as an effective barrier to pathogens. Two of the most common causes of paediatric admissions to UK hospitals are respiratory tract infections and gastroenteritis (175) (176). The skin may play a role in enhancing barrier immunity, through the actions of vitamin D, in organs with large surface areas and therefore exposure to the outside world.

This chapter will further explore the links between child respiratory health and the environment that affects it, and whether vitamin D has a role in mediating immune responses in the respiratory system. Analysis of the relationship between paediatric lower respiratory tract infection (LRTI) admission rates and meteorological factors will be carried out, using the same methodology as described in Chapter 2.

3.2 Background

3.2.1 Epidemiology of paediatric LRTI

Global estimates have consistently found acute LRTI to be a major cause of child mortality (177). In 2013, LRTIs were the leading infectious cause of death in all ages (ranking fifth overall), and the second biggest cause of disability-adjusted life years (DALYs) (178). Worldwide, there are between 1.4 and 1.8 million fatalities yearly due to pneumonia

(bacterial or viral infection of the lower airways) in children under 5 (179). In the UK, LRTI's also pose challenges to patient health and are a significant economic burden. Although it is hard to estimate, LRTIs constitutes a significant proportion of consultations within primary and secondary care, especially regarding paediatric patients (180). Almost all children will present to their GP with cough as the predominant symptom on at least one occasion before their 5th birthday.

3.2.2 Pathophysiology of LRTI

Acute LRTIs are defined as an infection of the respiratory tract below the vocal cords, lasting under 30 days and potentially affecting the bronchi, bronchioles or alveoli (116). Conditions encompassed by the term LRTI include: bronchiolitis, which entails acute inflammation and necrosis of the respiratory epithelium of bronchioles (smaller airways), or pneumonia, which describes inflammation of the terminal airways such as alveolar and respiratory bronchioles (181). Common viruses causing LRTI include rhinovirus, influenza virus, parainfluenza and respiratory syncytial virus (RSV). Other viral causes include adenoviruses, coronaviruses, paramyxoviruses, enteroviruses, human bocavirus and human metapneumovirus (42).

Viruses are more likely to cause primary pathology in children than bacteria; in the UK, infants and pre-school children can be expected to have between 6 and 10 infections per year due to respiratory viruses (181). Secondary bacterial infection is frequently seen as viral infection makes the lungs a susceptible environment due to epithelial damage and mucociliary dysfunction. Bacterial infection is commonly due to *Streptococcus pneumoniae* or *Haemophilus influenzae* (179). Vaccinations against *Haemophilus influenza* type B and pneumococci are available in the UK, as are seasonal influenza vaccines. However, the

influenza vaccine is not completely reliable and may offer different levels of protection in different seasons (177) (42).

3.2.3 Symptoms and management of LRTI

The common symptoms of LRTI in children are the consequence of challenges posed to the immune system by causative pathogens. Symptoms of LRTI may include a raised respiratory rate, which is the body's response to gas exchange becoming less efficient due to oedema and pus, leading to hypercapnia and lower oxygen (O_2) saturation of haemoglobin (182). The virus and the host immune response causes widespread local inflammation, resulting in local oedema, fever, recruitment of neutrophils which propagates the immune response, and pus formation alongside deposition of cellular and pathogen debris (42) (182).

An increased respiratory effort leads to recruitment of accessory respiratory muscles (used to aid breathing alongside the diaphragm and intercostal muscles used at rest), and in paediatric patients, recessions may be seen as a result of increased negative intrathoracic pressures acting on a weaker chest wall (183). Management of LRTI is often supportive, with antibiotics used in accordance with local hospital guidelines if a bacterial cause is suspected. Goals for LRTI management are somewhat age dependent and often focus on O_2 saturations, particularly during sleep, and sufficient nutritional intake before discharge (184).

3.2.4 Vitamin D, weather and LRTI

The impact of vitamin D on the innate immune system, as outlined in Chapter 1, has been found to be especially pertinent in the case of viral LRTI, where vitamin D deficient patients

have been found to be more vulnerable (116). Reactive oxygen species modulation, pattern recognition receptor inhibition and upregulation of IκB, β-defensins and cathelicidin production are mechanisms behind the anti-inflammatory, anti-viral actions of vitamin D in the respiratory system (42). An increased duration of sunlight exposure would provide more opportunity for paediatric populations to synthesize vitamin D.

Air temperature is another factor which has been shown to impact LRTI prevalence. This could explain the significant seasonal variation in LRTI-attributable morbidity and mortality, with more admissions to hospital in winter, particularly in children and the elderly (185) (186). Incidentally, vitamin D stores built up in the Summer (to varying degrees depending on environmental and individual factors) begin to deplete going into the Winter months. Colder weather is also correlated with lower levels of sunlight; when combined with the effect of covering up with warm clothes or remaining indoors, the ability to synthesize vitamin D, a mediator of LRTI admissions, could be behind this effect.

3.3 Methods

Admissions data from an NHS HES dataset was used. The International Classification of Disease, 10th revision (ICD-10) codes for LRTI admission were used: J10.0, J11.0/11.1 J12, J13, J14, J15, J16, J18.0, J18.1, J18.9 and J21 (Table 3.1). Data were collected for patients under the age of 16 admitted to hospital with LRTI, with annual indirectly age-gender standardised admission rates per 100,000 per annum calculated for the levels of each English government office region, strategic health authority (SHA), local authority (LA), and Primary Care Trust (PCT) (2011 boundaries used). Data were recorded firstly on April 1st

2002, then yearly from the same date until March 31st 2011. To match with Met Office weather data as accurately as possible, 150 PCT regions were mapped onto 6 Met Office regions, with averages taken to give 6 regional LRTI admission rates for each year.

Table 3.1- ICD-10 codes used in this LRTI HES dataset and their corresponding conditions

ICD-10 code	***Condition coded for***
J10.0	Influenza virus pneumonia
J11.0/11.1	Influenza with pneumonia/other respiratory manifestations, virus not identified
J12	Viral pneumonia, not elsewhere classified
J13	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Haemophilus influenzae
J15	Bacterial pneumonia excluding S. pneumoniae, H. influenza, Chlamydia, Legionnaires or congenital induced pneumonia
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J18.0	Bronchopneumonia unspecified
J18.1	Lobar pneumonia, unspecified
J18.9	Pneumonia, unspecified
J21	Acute bronchiolitis

The same meteorological data were used for this analysis as in Chapter 2, when examining the association between weather and asthma admissions. Total annual HoS, total annual rainfall (mm) and average annual air temperature (°C) were gathered from 6 Met Office regions (Figure 3.1) using synoptic data from weather stations. As described in Chapter 2, the Met Office data were manipulated so that the data represented annual weather variables starting on the same date as the HES data. Therefore, the same methods and formula were used in this investigation into LRTI admissions as in Chapter 2, to give an April to March annual report. Socioeconomic deprivation was included as a covariate in the statistical model, using regional Income Deprivation Affecting Children Index (IDACI) scores.

Statistical analysis was undertaken using multivariate linear regression and an extended generalised estimating equation, the same adapted Davies *et al* method as was used in the previous chapter (143). Included in the regression model was LRTI admission rate, HoS, rainfall, temperature and IDACI. STATA version 8.0 (STATA Corp, Texas, USA) was used to carry out the analyses.

Figure 3.1- Map of climate districts used to calculate climate data averages in England and Wales (259)

3.4 Results

The number of emergency admissions of children under 16 admitted to hospital in England with LRTI between 2002/3 and 2010/11 was 314,226. The lowest annual number of LRTI admissions in England was 29,773 in 2002/3, the highest being 42,842 in 2010/11 and it increased every year on record. The English child population ranged from 9,654,027 in 2007/8 to 9,853,580 in 2002/3.

Matched PCT averages of LRTI admission rates gave 6 regional age-gender corrected LRTI admission rates per 100,000 per annum for each of the 9 years of the study. The mean LRTI admission rate for all regions and years was 390.0 per 100,000 per annum, with the median

rate being calculated as 396.7 per 100,000 per annum. The lowest regional LRTI admission rate was 248.7 per 100,000 per annum in England Southeast & Central in 2008, with the highest rate being 554.9 per 100,000 per annum in England Northwest & North Wales. Brighton and Hove City PCT had the lowest LRTI admission rate on PCT level with 44.76 per 100,00; City and Hackney Teaching PCT had 5 of the 10 lowest PCT admission rates in the country. Sheffield PCT had the highest LRTI admission rate with 913.80 per 100,000 per annum.

As detailed in Chapter 2, the mean HoS for all years and regions recorded by the Met Office was 1560.8, with the median being 1548.2. England Northwest & North Wales was the Met Office region receiving the least annual HoS, giving the lowest value of 1320 HoS in 2004/5. England Southeast & Central was the region with the most HoS in 2006/7. The average total annual rainfall was 920.6mm and the median was 830.8mm. East Anglia saw the lowest annual rainfall of 534.7mm in 2005/6; the highest annual level of rainfall was seen in England Northwest & North Wales, with 1563.8mm of rain falling in 2008/9. For all regions and years, the average temperature was 10.0°C, and the median temperature was 10.1°C. The lowest average temperature was 8.24°C in England Northwest & North Wales in 2010/11, whereas the highest average temperature was 11.2°C in England Southeast & Central in 2006/7.

Figure 3.2, Figure 3.3 and Figure 3.4 show visual representations of the crude relationships between LRTI admission rates and meteorological factors. LRTI admission rates decrease as the total annual HoS and average temperature increase, whereas both rainfall and LRTI admission rates are shown to increase together.

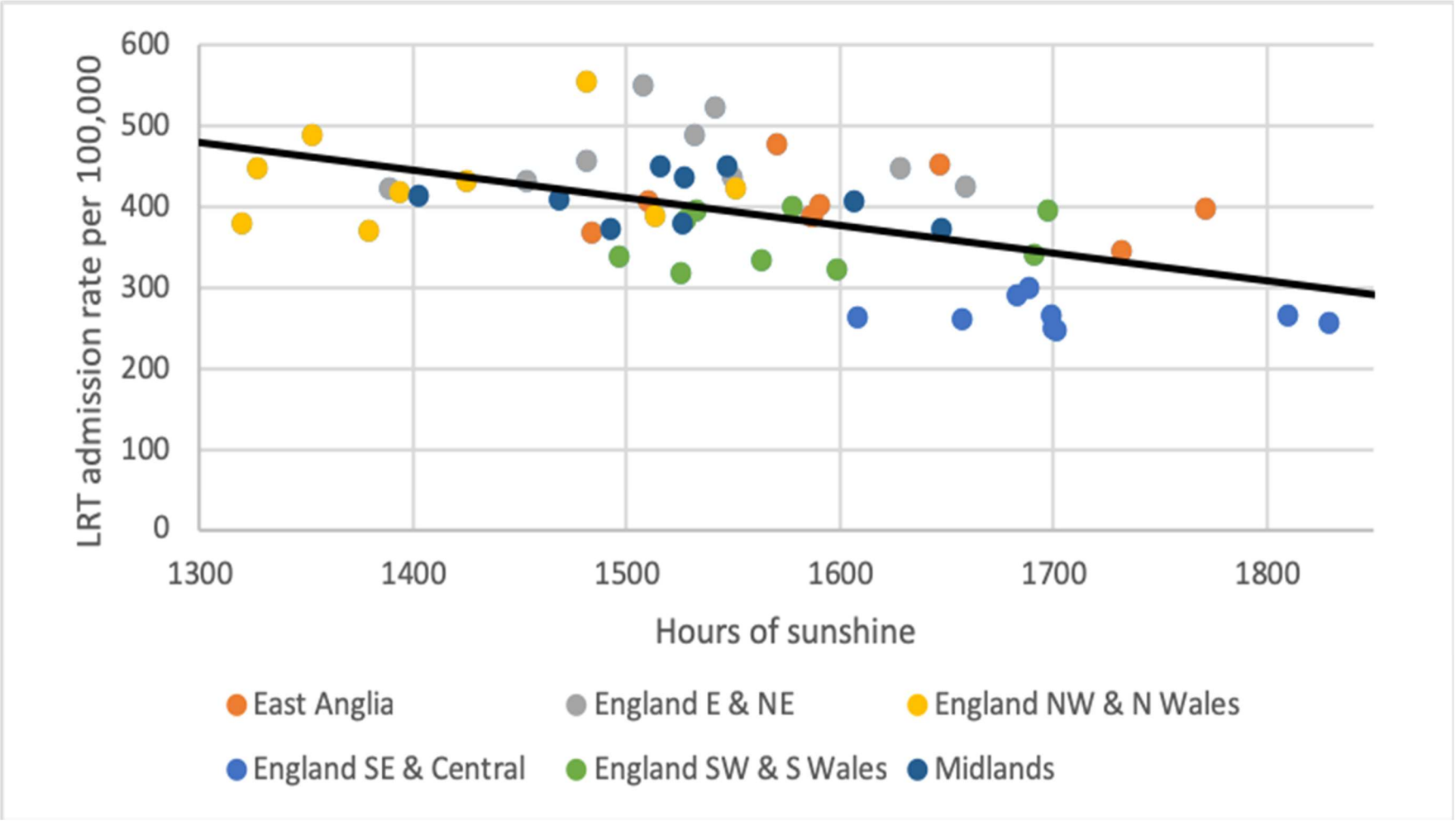

Figure 3.2- Scatter graph showing LRTI admission rates and hours of sunshine in 6 Met Office regions

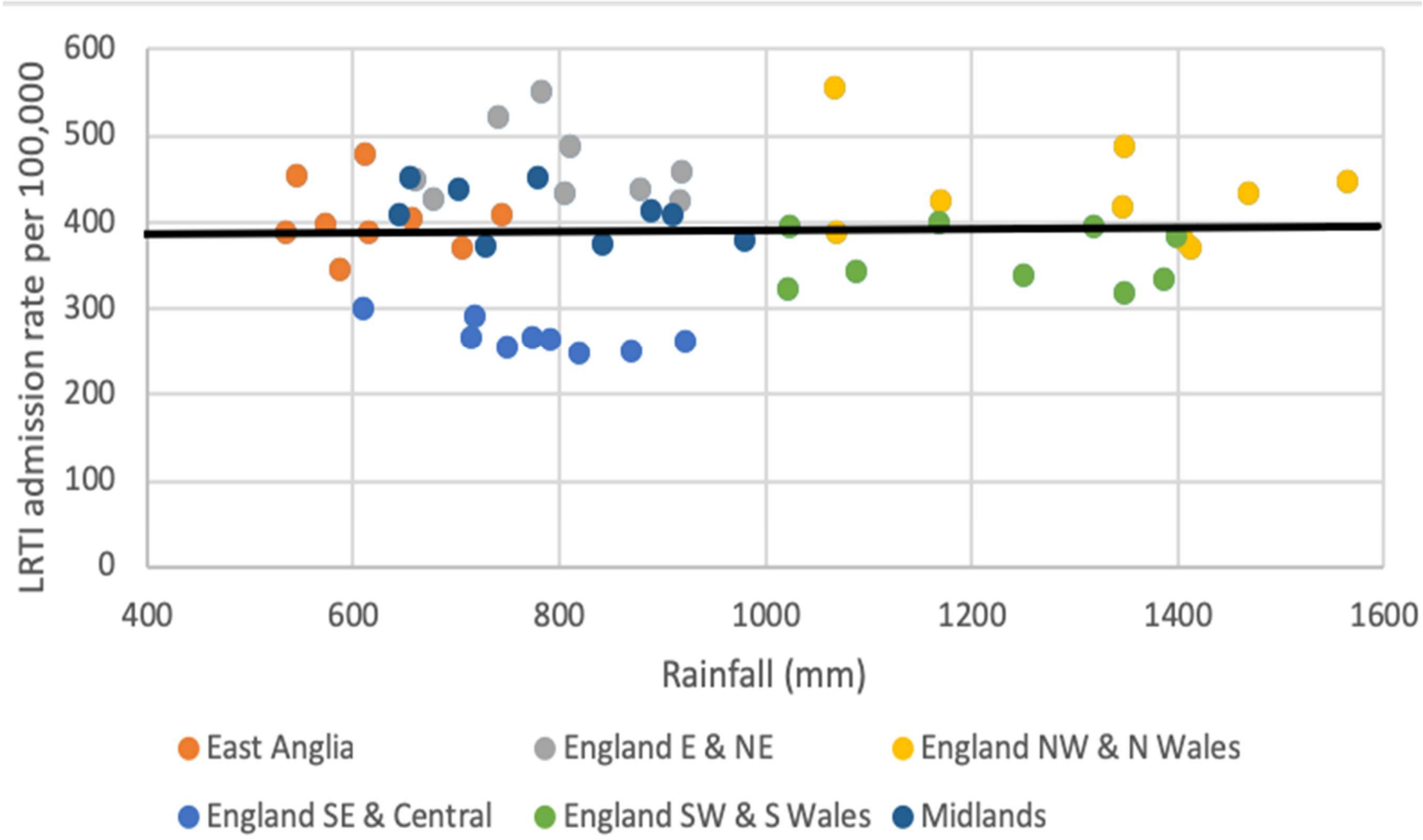

Figure 3.3- Scatter graph showing LRTI admission rates and rainfall in 6 Met Office regions

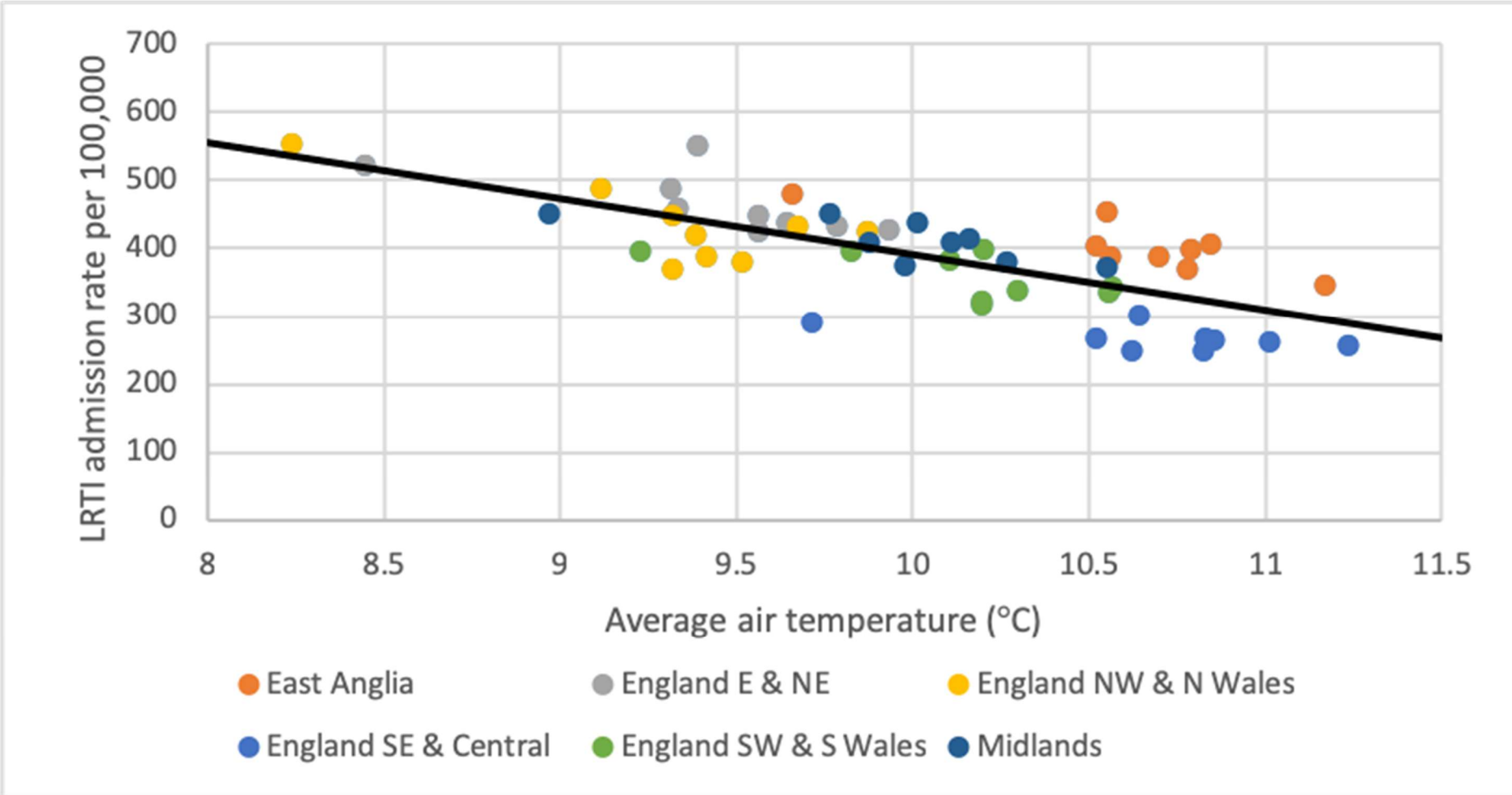

Figure 3.4- Scatter graph showing LRTI admission rates and temperature in 6 Met Office regions

Table 3.2- Univariate linear regression analysis of the association between LRTI admission rates per 100,000 per annum and hours of sunshine

	LRTI admission rate per 100,000 per annum			
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**
Hours of sunshine	-0.342	-0.491, -0.193	<0.001	0.2764

Adjusted R^2 (variance) = 0.2764

Table 3.3- Analysis of the association between LRTI admissions and meteorological factors using a linear regression model

	LRTI admission rate per 100,000 per annum			
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**
Hours of sunshine	-0.229	-0.354, -0.103	<0.001	-3.66
Rainfall	0.114	-0.159, -0.0699	<0.001	-5.17
Temperature	-81.2	-100, -61.6	<0.001	-8.35
IDACI score	-6.34	-9.17, -3.52	<0.001	-4.51

Adjusted R^2 (variance) = 0.7518

Table 3.3 shows the results of the linear regression model, with all variables included found to be significantly associated with LRTI admission rates. This model demonstrates that 100 additional HoS associate with a reduction in annual paediatric LRTI admission rates 22.9 per 100,000 per annum (5.87% reduction of the mean rate). Every additional 100mm of rainfall is associated with higher admission rates, 11.4 per 100,000 per annum (2.92% increase of the mean rate). Every degree (°C) increase in annual average temperature associates with a reduction in LRTI admission rates by 81.2 per 100,000 per annum (20.8% reduction of the mean rate) and regional IDACI scores increasing by 0.1 associates with a reduction in LRTI admission rates by 6.34 per 100,000 per annum (1.63% reduction of the mean rate). The

adjusted R^2 value of 0.7518 shows that 75.18% of all LRTI admissions in English children can be accurately described using this model.

Table 3.4- Results from extended generalised estimating equation, showing the associations between LRTI admissions and meteorological factors

	LRTI admission rate per 100,000 per annum			
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**z statistic**
Hours of sunshine	-0.265	-0.401, -0.129	<0.001	-3.81
Rainfall	0.133	-0.167, -0.0982	<0.001	-7.54
Temperature	-92.2	-117, -67.8	<0.001	-7.42
IDACI score	-6.76	-8.95, -4.57	<0.001	-6.06

Wald $chi^2(5)$ =265.96, Scale parameter=1329.278

The results from the extended generalised estimating equation are shown in Table 3.4; all variables remain significantly associated with LRTI admission rates in the model, with coefficients also increasing in magnitude for all variables. The Wald chi^2 test result of 265.96 with 5 degrees of freedom shows the null hypothesis, that none of the variables have a significant association with LRTI admission rates, can confidently be rejected, and that the statistical results from this model accurately reflect the relationships at play in this study period. The scale parameter of 1329 shows that the distribution is widely spread out.

3.5 Discussion

The associations seen in our analyses between LRTI admission rates and weather variables are independently significant in real and relative terms. Hours of sunshine has a strong inverse association with admissions for LRTI in children. The increased exposure of regional child populations to ultraviolet-B (UVB) radiation in higher durations of sunlight would

improve the ability of children to reach a sufficient vitamin D level, which in turn improves anti-viral respiratory responses.

Compared to the relationships found in Chapter 2 between weather and asthma admissions, LRTI admissions were sensitive to changes to a wider range of meteorological factors than just HoS. Seasonality was controlled for by using annualised weather and admissions data, therefore the increase in regional LRTI admissions seen in colder weather is not due to the higher incidence of viral infection in winter months. The statistical association between LRTI admissions and temperature and rainfall are also strong. Cold or rainy weather would both cause individuals to cover their skin more and go outdoors less but if this was the explanation, we would have been likely to see an effect in asthma admissions too. As vitamin D deficiency is a medium-term, often subclinical condition, there is a lesser potential for there to be reverse causality with acute LRTI, which by definition last less than 30 days.

Univariate linear regression analyses of both rainfall and temperature with hours of sunshine (HoS) showed high rainfall and cold temperatures to be negatively associated with HoS. In other words, the one weather variable appears to interact with another and perhaps should not be considered as truly independent variables. Unsurprisingly perhaps, regions in England with more sunshine are warmer and drier.

However, the observed effects have some biological plausibility. It has been theorized that lower temperatures independently impede the actions of the respiratory immune system; vasoconstriction of the blood vessels in the nose, which occurs as a result of lower ambient temperatures and an attempt to conserve body heat, leads to a reduced filtering capacity of

the nose, deeper penetration of respiratory viruses and symptom development from previously sub-clinical viral infection (187) (188). Another explanatory mechanism for cold temperatures increasing viral infection rates is that viruses survive for longer in these conditions (185). Factors such as smoking and pollution have previously been shown to make children more susceptible to LRTI, and both are linked strongly with socioeconomic deprivation and are likely to form part of the explanation behind the strong relationship found between IDACI and LRTI admission rates in this model (189) (190).

3.5.1 Strengths and limitations

As discussed in Chapter 2, there are limitations to using this Met Office and HES data, but on balance the large population it provides data from and the improving quality of data sufficiently compensate for this. There are many ICD-10 codes which the HES dataset defines as LRTI and generates admission rates from and usually there would be concern that this would lead to an overestimation of admission rates. However respiratory infections are relatively common and easy to diagnose and not casting such a wide net in defining LRTI would risk omission of LRTI cases.

Using total annual HoS instead of average daily sunshine duration is unlikely to be a limitation of this analysis. Firstly, a limitation of using HoS data is that this does not describe how much sunshine the child population is exposed to. Behavioural studies have shown that those who spend more time in the sun have more optimal vitamin D statuses (86). This study aims to use HoS as a marker of population vitamin D status. Vitamin D synthesis is an efficient process, with short daily exposures to adequate UVB radiation often being sufficient. Therefore, monthly or annual sunlight data would probably be as informative as

average daily sunshine duration. This could also be true for total annual rainfall, however there is a far higher upper limit for how much rain can fall in individual days or weeks than there is for HoS in a day and the data is therefore more vulnerable to anomalous data. This analysis may have benefitted, therefore, from using average total daily or weekly rainfall. However, the large scale of this population study, with millions of children constituting the study population and the network of national weather stations used to generate regional weather data, makes it likely that any effects from anomalous data are compensated for.

Examining the relationship between weather and child health may be more insightful when using data collected at smaller aggregate levels. Large regions may over-generalise the likely heterogenous health profiles of different communities and health economies. Clinical commissioning group admissions data may be useful to analyse, as these groups are set up to manage population health outcomes at a more granular level.

Another limitation of this analysis is that the varying quality of the sunshine the Met Office provides data for is not described in the data. In winter months and at higher latitudes, a cloudless sky all day is likely to provide very little vitamin D for the population when compared to regions at lower latitudes in summer time. This is a limitation of using HoS data as a proxy for examining the potential vitamin D status of a population. UVB levels would provide a more direct causal pathway to investigate. Controlling for factors which attenuate UVB radiation intensity such as cloud cover and altitude would further improve the quality of the research in this way. Population ethnicity is another factor affecting the threshold required for UVB levels to reach before vitamin D can be efficiently synthesized and would be useful to control for in an ecological study such as this.

3.5.2 Implications for clinical practice

The ability of children to synthesize vitamin D has been found to be important to respiratory health on a population level. Since LRTIs are acute conditions, risk management and prevention especially in vulnerable children are important objectives for clinicians and parents. Advice concerning sun screen application, as discussed in Chapter 2, applies in the context of LRTI risk reduction. Sunlight exposure should be encouraged, however from this analysis it is also important for children to be protected from cold temperatures. This might be a difficult balance to make as wrapping up warm involves reducing skin exposure to sunlight. However, in the winter months when cold weather is more prevalent, sunlight is very unlikely to provide adequate levels of UVB radiation to catalyse vitamin D synthesis. Therefore, protection from cold air should have more potential to reduce LRTI risk.

A recent systematic review and meta-analysis of individual participant data has found that vitamin D supplementation reduced participants experiencing at least 1 LRTI (number needed to treat (NNT=33) (191). A Cochrane review found vitamin D to prevent asthma exacerbations requiring admission (NNT=27) (121). In this respect, the findings from chapter 2 and 3 are concordant with the literature. It can be estimated that an additional 100 hours of sunshine reduces LRTI admission rates by 5.87% and asthma admission rates by 9.31% relative to the mean. This supports the argument that population sunshine exposure is linked with overall vitamin D status.

3.6 Summary

In this chapter, the effects of environmental factors on LRTI have been examined. The pathophysiology of LRTI and previously identified environmental targets of this have been explored in greater depth. In the analyses carried out in this chapter HoS, lower rainfall and warmer temperatures were all found to be significantly negatively correlated with paediatric hospital admissions with LRTIs annually in English regions. As in the case of acute asthma admissions, socioeconomic deprivation is significantly linked with higher LRTI admission rates.

4 The impact of weather on gastroenteritis

4.1 Introduction

The previous two chapters of this thesis have focused on the interactions between child populations' environment and their respiratory health. Vitamin D is a proposed mediator of changes to pathologies affecting the respiratory immune system, namely asthma and LRTI, and the two subsequent chapters will seek to assess the how likely the validity of this proposition is. In this chapter, there will be a shift in focus to examine the impact of weather on paediatric pathology in the gastrointestinal tract. Gastroenteritis as a disease will be summarised, as will the environmental determinants of the development and severity of the condition. Analysis will be carried out to assess the presence and strength of associations between meteorological variables and paediatric gastroenteritis admissions in England.

4.2 Background

4.2.1 Gastroenteritis: pathogens and population health

Acute gastroenteritis in children is caused by viruses in the majority of cases (192). The most common virus to cause gastroenteritis is rotavirus; others include calicivirus, adenovirus and astrovirus (193). Upon infection, the epithelial and immune cells of the intestinal mucosa mount an immune response which, along with various viral enterotoxins, cause symptoms of diarrhoea and vomiting which can lead to dehydration (193) (194).

Dehydration due to fluid loss in this way can be fatal; globally between 1.4 and 2.5 million children under 5 years old die due to diarrhoeal disease. Approximately 525,000 of these cases are attributable to environmental factors (195) (196).

In the UK, around 20% of GP consultations for children under 5 are attributable to gastroenteritis; combined with hospital admissions this incurs significant economic costs, estimated £11.5 million per year in 2007 (195). It has been estimated that 88,000-113,000 UK hospital beds are closed due to gastroenteritis each winter (197). In Western countries such as the UK, rotavirus is the cause of approximately 87% of acute gastroenteritis cases, and in July 2013 vaccinations against rotavirus were introduced the child population at 2 and 3 months of age (192) (198). Gastroenteritis cases in GP settings decreased by 15% overall, with a 41% reduction in months with historically high rotavirus circulation (198). Across GP, A&E and hospital ward settings, in children under 5 around 87,000 acute gastroenteritis patient contacts were averted in 2013/14, saving an estimated £12.5 million in healthcare costs.

4.2.2 Immune responses to gastroenteritis

The gastrointestinal tract has many immune defence mechanisms. Gastroenteritis has faeco-oral transmission; after surviving the low pH of stomach acid and enzymatic stress, pathogenic viruses, bacteria or their toxins have to overcome the gut mucosa's barrier immunity (199). Pathogenic bacteria also have to compete with the gut microbiome to survive. Rotavirus, the most common causative pathogen of acute gastroenteritis in children under 5, is a double strand DNA (dsDNA) virus (199) (200). Non-structural protein-4 (NSP4) is a viral enterotoxin which activates luminal chloride pumps, drawing water out of enterocytes and into the intestinal lumen (200).

The enteric nervous system is also activated by the effects of NSP4: serotonin (5-HT) is secreted by endocrine enterochromaffin cells in response to an NSP4-induced increase intracellular calcium level, and then this serotonin then stimulates enteric nerves and increases intestinal motility (200). When internalised into mature enterocytes of the small intestine, rotavirus is detected by toll-like receptor (TLR) 3 and retinoic-acid inducible gene (RIG)-like receptors, which upregulate inflammatory responses via nuclear factor kappa-B (NFκB) and interferon regulatory factor-3 (IRF3) (199) (201). Pro-inflammatory cytokines are produced, with type 1 interferons (α and β) acting on the original and adjacent enterocytes (autocrine and paracrine actions) to upregulate receptors sensitive to virus components and further interferon production (201). Interferons are key to the anti-viral defence of the gastrointestinal tract, so much so that rotavirus has evolved a mechanism to subvert interferon signalling (202).

The innate pro-inflammatory response to enteric viruses exacerbates the loss of function of the affected tissues and worsens patient symptoms (199). Healthy gut microbiota and long-term immunity reduce the risk of symptom development and severity of gastroenteritis (199). The main treatment goal of gastroenteritis is rehydration, which is commonly achieved in the UK via oral or intravenous rehydration therapy (193). Anti-emetics such as ondansetron can be used to augment treatment but are not always essential (193).

4.2.3 Environmental factors' impact on gastroenteritis

While increased levels of sunlight might allow vitamin D to modulate the innate anti-viral responses seen in gastroenteritis via the mechanisms discussed in chapters 1 and 2, there are other potential targets for environmental factors in this disease process. Colder

temperatures have previously been shown to lead to an increased risk of gastroenteritis in young children (203) (204). This may be due to enteroviruses such as rotavirus having optimal survival duration at colder temperatures, it is theorised that infection rates increase in winter as more viruses remain intact on surfaces for children to touch then infect themselves and each other (203). Atchison *et al* found that there was a 13% decrease in reported infections for every 1°C increase in temperature above a threshold of 5°C (203). In this study, no associations were found between rainfall and gastroenteritis admissions (203). There is very little further evidence examining the relationship between gastroenteritis and other environmental factors such as pollution or hours of sunshine.

4.3 Methods

HES data were used to describe data collected in English NHS hospitals admissions with acute gastroenteritis in children under 5 between April 1st 2002 and March 31st 2011. When a patient was admitted and coded with ICD-10 specified conditions (listed in Table 4.1), covering viral, bacterial or other acute gastrointestinal infections, they were recorded in this HES dataset. In this dataset, age and gender standardised admission rates were indirectly calculated for each year on the level of government office region, strategic health authority, local authority and PCT.

Table 4.1- ICD-10 codes used in this gastroenteritis HES dataset and their corresponding conditions

ICD-10 codes	Conditions
A02.0	Other salmonella infections
A04.-	Other bacterial intestinal infections, excluding tuberculous enteritis
A05.9	Bacterial foodborne intoxication
A07.2	Cryptosporidiosis
A08.0	Rotaviral enteritis
A08.1	Acute gastroenteropathy due to Norwalk agent
A08.2	Adenoviral enteritis
A08.3	Other viral enteritis
A08.4	Viral intestinal infection, unspecified
A08.5	Other specified intestinal infections
A09	Other gastroenteritis and colitis of infectious and unspecified origin
K52.0	4.3.1.1.1 Gastroenteritis and colitis due to radiation
K52.1	Toxic gastroenteritis and colitis
K52.2	Allergic and dietetic gastroenteritis and colitis
K52.8	Other specified noninfective gastroenteritis and colitis
K52.9	Noninfective gastroenteritis and colitis, unspecified

Open access Met Office datasets were used to create weather variables for six meteorological regions in England and Wales (Figure 3.1). Each PCT was matched to its corresponding meteorological region, and for each one average gastroenteritis admission rates calculated. Weather variables included in this analysis were total annual hours of sunshine (HoS), total annual rainfall and average temperature. Regional Income Deprivation Affecting Children Index scores were used to control for the potential confounder of deprivation.

Continuing the methodology used in previous chapters, multivariable linear regression was used to analyse these data, in addition to an extended generalised estimating equation. STATA version 8.0 (STATA Corp, Texas, USA) was used to undertake these statistical analyses.

Figure 4.1- Map of climate districts used to calculate climate data averages in England and Wales (259)

4.4 Results

During the 9-year study period, 328,837 children under 5 years old were admitted to hospital with gastroenteritis. Annual admission rates in England ranged from 31,980 in 2003/4 to 40,575 in 2009/10. The child population of England, from which admission rates were calculated, ranged from 2,849,444 to 3,267,092. The mean acute gastroenteritis admission rate for all regions and years was 1375 per 100,000 per annum, and the median was 1367. The PCT-level admission rates ranged from 38.7 per 100,000 per annum in Brighton and Hove PCT to 386.3 per 100,000 per annum in Stoke-on-Trent PCT. Descriptive statistics of these weather variables are discussed in Chapter 3. Visual representations of the relationships between gastroenteritis admission rates and both HoS and temperature variables (below) indicate that lower regional temperatures and sunlight exposure occur with higher admission rates (Figure 4.2, Figure 4.4).

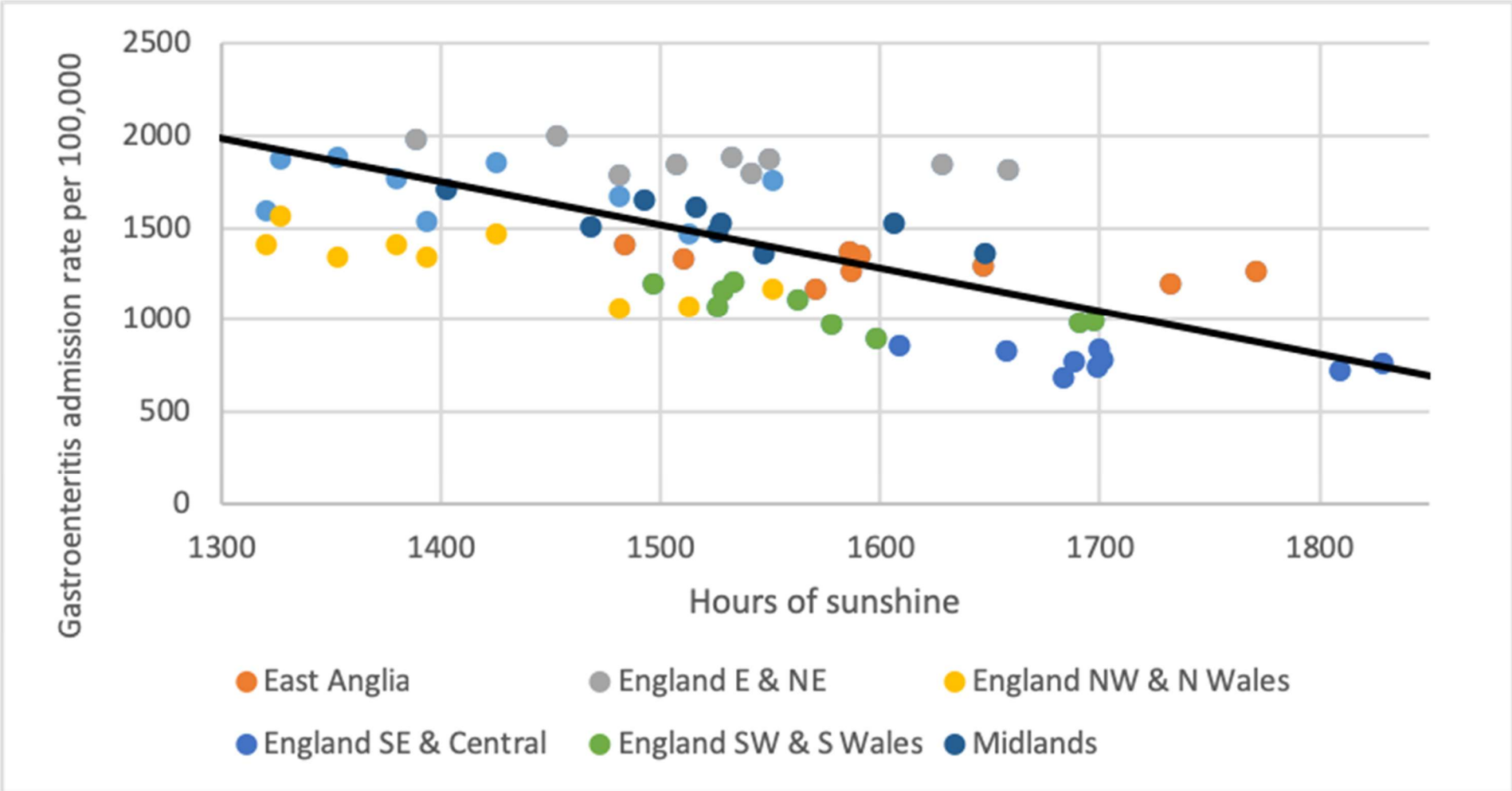

Figure 4.2- Scatter graph showing gastroenteritis admission rates and hours of sunshine in 6 Met Office regions

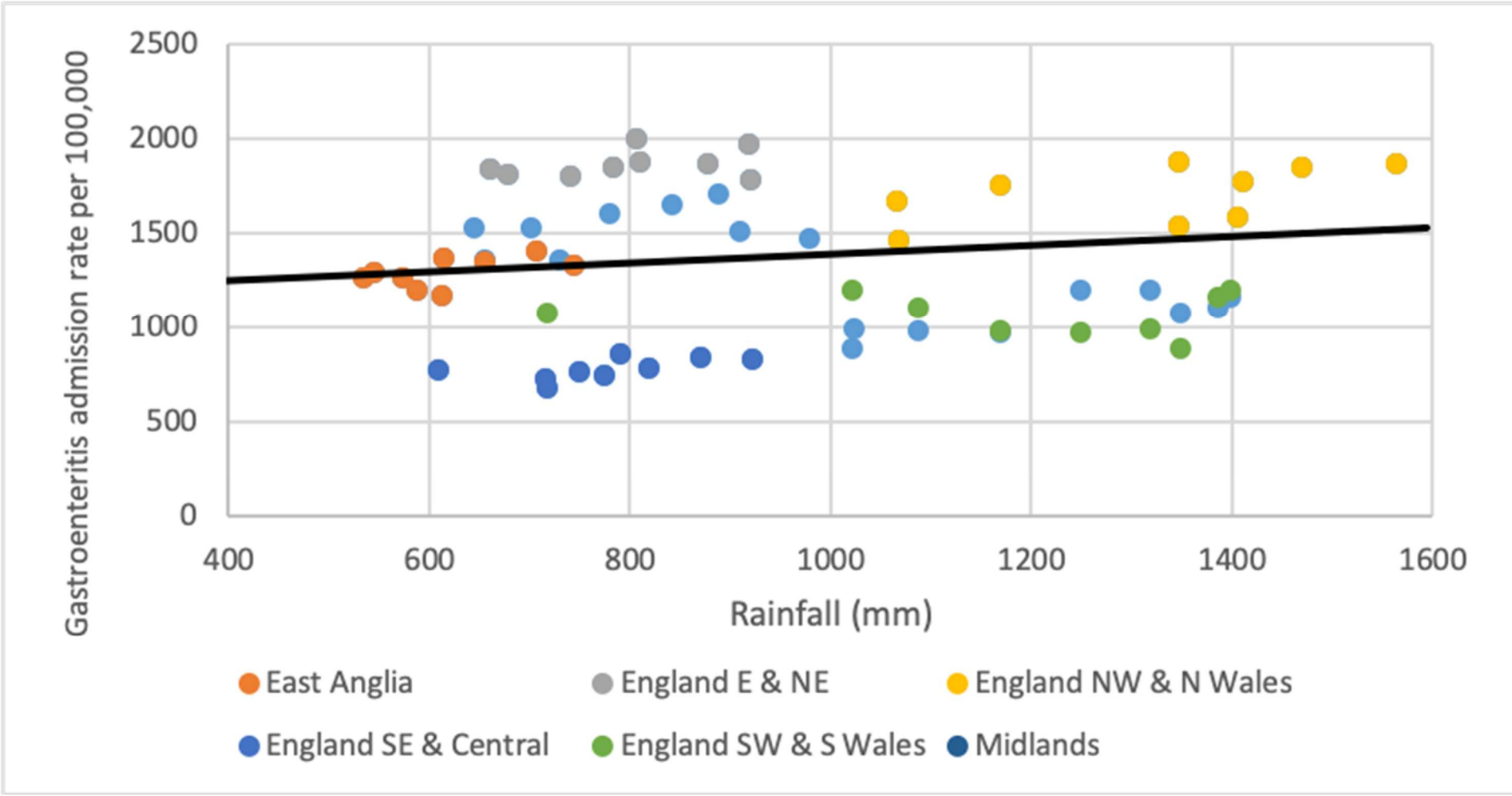

Figure 4.3- Scatter graph showing gastroenteritis admission rates and rainfall in 6 Met Office regions

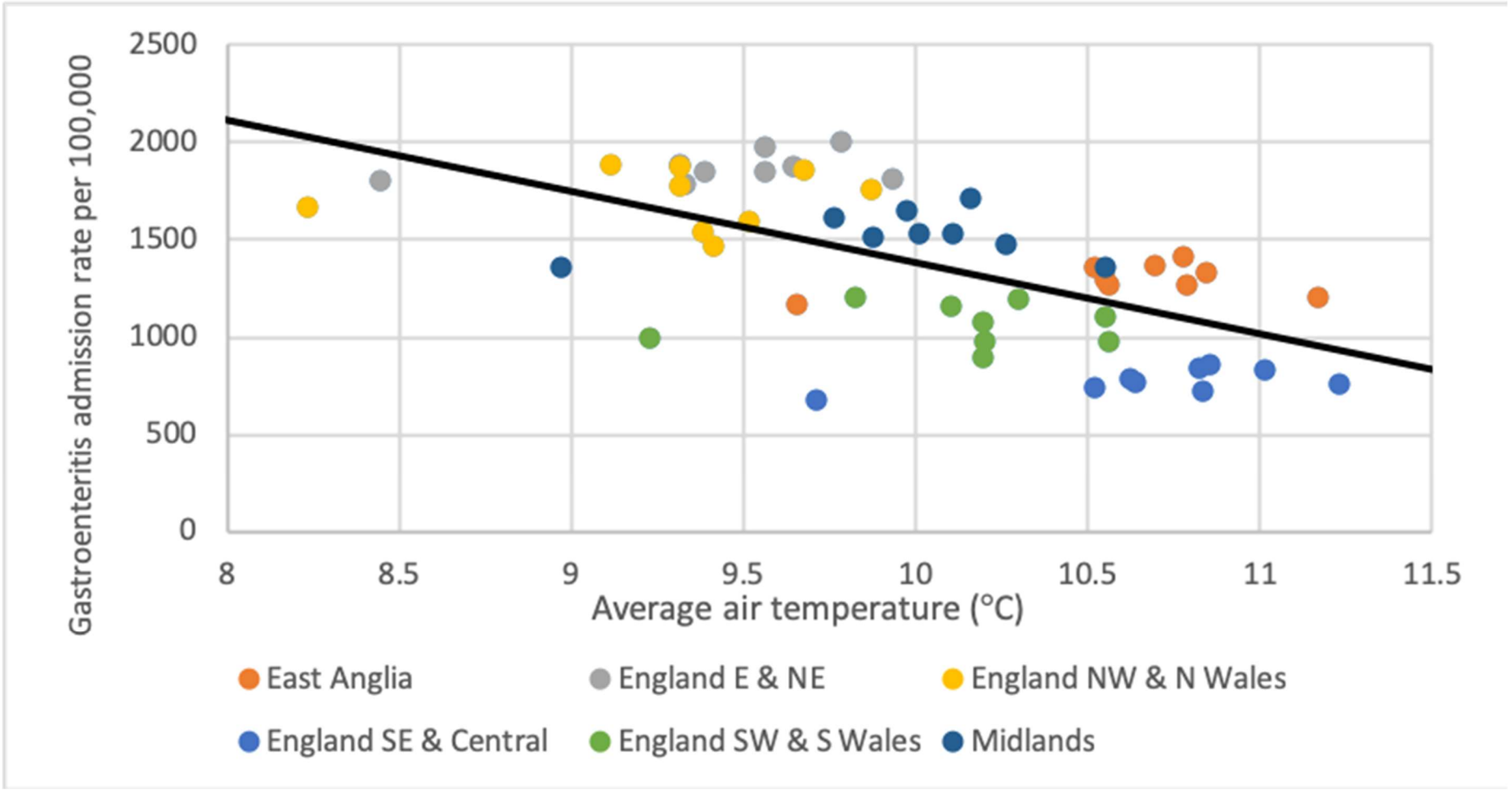

Figure 4.4- Scatter graph showing gastroenteritis admission rates and average air temperature in 6 Met Office regions

The results of the linear regression model are shown in Table 4.3. The meteorological variables included in this model: HoS, rainfall and temperature, were all found to be significantly associated with gastroenteritis admissions in children under 5 years old. According to the linear regression model, every 100 additional hours of sunshine a region receives annually is associated with a reduction in the acute gastroenteritis admission rate by 241 per 100,000 per annum, a 17.5% reduction relative to the mean rate. Every additional 100mm of rainfall associates with a decrease in admission rates by 49.4 per 100,000 per annum, a 3.59% reduction relative to the mean rate. Each degree (°C) that the average annual air temperature increases is associated with a reduction in gastroenteritis admission rates by 185 per 100,000 per annum, a 13.5% reduction relative to the mean rate. According to the results of this linear regression model, socioeconomic deprivation was not found to be significantly associated with gastroenteritis admission rates.

The extended generalised estimating equation (GEE) gave results which showed all weather variables to be significantly associated with gastroenteritis admission rates (Table 4.4). While controlling for dislinearity of variables strengthened the magnitude of rainfall and temperature's impact on admission rates, the regression coefficient for hours of sunshine instead decreased the magnitude. Socioeconomic deprivation (IDACI) was deemed to be significant by this statistical test. A Wald chi^2 test result of 485.93 with 5 degrees of freedom shows a strong link between the results of this study and the real situation in the study period. The scale parameter of 75,956 shows that the distribution examined was widely distributed.

Table 4.2- Univariate linear regression analysis of the association between gastroenteritis admission rates per 100,000 per annum and hours of sunshine

	Gastroenteritis admission rate per 100,000 per annum			
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**
Hours of sunshine	-2.35	-3.00, -1.69	< 0.001	-7.20

Adjusted R^2 (variance) = 0.398

Table 4.3- Analysis of the association between gastroenteritis admissions and meteorological factors using a linear regression model.

	Gastroenteritis admission rate per 100,000 per annum			
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**
Hours of sunshine	-2.41	-3.22, -1.60	<0.001	-6.00
Rainfall	-0.494	-0.780, -0.208	<0.001	-3.47
Temperature	-185	-310, -59.7	<0.001	-2.97
IDACI score	0.968	-17.2, 19.1	0.915	0.11

Adjusted R^2 (variance) = 0.6253

Table 4.4- Results from extended generalised estimating equation, showing the associations between gastroenteritis admissions and meteorological factors

	Gastroenteritis admission rate per 100,000 per annum			
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**z statistic**
Hours of sunshine	-1.61	-2.28, -0.936	<0.001	-4.68
Rainfall	-0.757	-0.907, -0.608	<0.001	-9.93
Temperature	-567	-690, -444	<0.001	-9.04
IDACI score	-12.3	-21.8, -2.67	0.012	-2.50

Wald $chi^2(5)$ =485.93, Scale parameter=75,956.25

4.5 Discussion

The effect of hours of sunshine on child population health has been shown to extend to a prominent extra-respiratory disease. It can be inferred from these results that children's immune defence against gastroenteritis is sensitive to all weather variables included in the model. The time period of 2002-2011 was before the introduction of the rotavirus vaccine in 2013, therefore any trends in admission rates are not due to vaccination.

Average air temperature was a particularly potent determinant of gastroenteritis admission rates, with the results of the linear regression and extended GEE both giving coefficients of great magnitude. There could be several explanatory mechanisms contributing to this effect. As described before, colder temperatures have been shown to reduce rotavirus infection rates, with this effect attributed to the increased likelihood of viruses surviving on surfaces, thereby increasing the chance of children becoming infected (203). Even with HoS present in this model, temperature remains a significant determinant of admissions, therefore there is likely some independent interaction of temperature alone on gastroenteritis admissions.

The extended GEE did find IDACI scores to be significantly associated with acute gastroenteritis admissions ($p=0.012$), whilst the linear regression model showed no relationship. The lack of a linear association implies that the factors associated with deprivation that could potentially affect admission rates, for example smoking rates, pollution or access to healthcare, have little impact on the infectious disease and/or the immune response to it (205) (168). Nevertheless, while the regression model assumes that the relationship is linear, the extended GEE does not. One could therefore argue that

deprivation is less likely to be associated with gastroenteritis admission rates than HoS, for example.

Regional duration of sunshine exposure was significantly associated with acute gastroenteritis admissions in real and relative terms. The percentage decrease in admissions for gastroenteritis in English child populations due to HoS was around twice the reductions found in chapters 2 and 3 which focused on asthma and lower respiratory tract infection (LRTI) admission rates. It can be interpreted from these results that the ability of a largely unsupplemented population of children to synthesize vitamin D is paramount to the capacity to mount an effective anti-viral defence. The bolstered innate immune system in relatively sunnier regions, alongside with a decreased viral infection rate in relatively warmer regions could explain the robust improvement in acute gastroenteritis admission rates in paediatric populations.

Little research currently exists which investigates the effect of vitamin D or its deficiency on gastroenteritis. One study in Colombia found that vitamin D-deficient children were around twice as likely to experience diarrhoea and vomiting as their peers (206). Another study carried out in India found no increase in diarrhoea symptoms in vitamin D deficient children (207). One study exploring the effects of quarterly vitamin D supplementation on diarrhoeal illness in Afghani children found no significant effect (208). Countries such as the UK have similar viral gastroenteritis rates, however the increased prevalence of bacterial, protozoan and parasitic causes limits the generalisability of results from existing studies to UK populations (193). The results of the population study described in this chapter serve as an

indicator that more research into this area could illuminate the effects of vitamin D on gastrointestinal health.

4.5.1 Strengths and limitations

Strengths and limitations of the data used in these analyses are discussed in previous chapters. The large scale of this study is both strength and limitation; the large sample size gives statistical power to more representative results, however averages taken of smaller aggregate levels may lead to a loss of detail and impact the generalisability and accuracy of the findings. To more directly investigate the impact of estimated population vitamin D status, the relationship between UVB radiation and gastroenteritis admission rates could be studied. A limitation for all ecological studies is ecological fallacy: associations found on macroscopic population levels may not be applicable to individuals. With so many physiological and environmental factors that impact vitamin D status and gastrointestinal health, this limitation would certainly apply to this study. There is also a limit to how many individual factors such as ethnicity, behavioural factors or gut microbiome that can be controlled for in a model using such large population data. However, the associations found in these analyses are particularly strong considering the many factors at play and potential sources of error.

4.5.2 Implications for clinical practice

It is useful for clinicians to be aware of the local environment their patients are exposed to, and what this means for their health. Gastroenteritis admissions in children aged under 4 have been shown to increase in association with less geographical sunlight exposure, colder temperatures and higher rainfall. Despite more research required to support the

recommendation of vitamin D supplementation to reduce the risk of infection, there are some considerations to be drawn from the relationships identified in this chapter.

While there is little use in suggesting parents move to a warmer, sunnier climate with their children during consultations regarding the prevention of gastrointestinal disease, there are several messages from these analyses worthy of note for clinicians. Exposure to sunlight outside of the 'vitamin D winter' (November-February each year) is helpful to suggest to aid vitamin D status, as is year-round supplementation (12) (209). As discussed in Chapter 2, sunscreen should be applied judiciously and is often unnecessary for short sunlight exposures (76).

Young children frequently contract viral infections from their peers and family, and transmission of common enteric viruses via the faeco-oral route is unlikely to be realistically avoidable. It remains to be seen whether younger children who follow DoH advice and actually take vitamin supplements are less prone to gastroenteritis or other early childhood infections.

4.6 Summary

The analyses in this chapter have confirmed that sunlight exposure and other weather variables are significantly associated with annual acute gastroenteritis admission rates. Gastroenteritis as a prominent paediatric health condition has been detailed, as has the pathophysiology leading to symptom development and immune responses. The findings in this chapter support the hypothesis that sunlight exposure leads to augmentation of innate

anti-viral immune responses by improving population vitamin D status. The impact of deprivation on gastroenteritis admissions is less pronounced than when compared to asthma or LRTI admission rates.

In the two chapters subsequent to this, more detailed investigations of the relationships between environmentally determined vitamin D status and child respiratory health will be undertaken. Asthma and LRTI admission rate HES data collected from a GP practice level will be analysed alongside UVB radiation doses of the wavelengths specific to vitamin D synthesis, correcting for other meteorological factors, smoking rates and deprivation affecting children.

5 Ultraviolet B Radiation and Asthma

5.1 Introduction

Vitamin D has been synthesized in organisms for millions of years; *Emiliania huxleyi*, a single celled eukaryotic species of phytoplankton that has existed for around 750 million years which has no calcified skeleton, has been found to convert its ergosterol into previtamin D when exposed to ultraviolet B (UVB) radiation (2) (210). Vitamin D is an ancient hormone, the by-product of a primordial sunscreen which has been harnessed by organisms evolving physiological processes such as immunomodulation and calcium metabolism. It helped sustain life when UVB radiation threatened the integrity of DNA, and eventually enabled land vertebrates to absorb and retain adequate calcium to mineralise their bones (2).

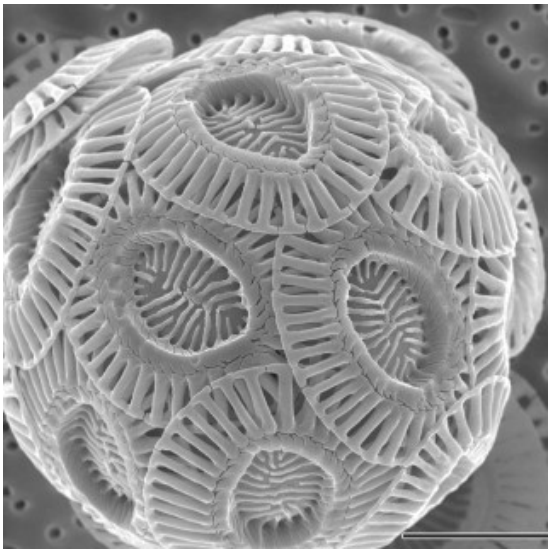

Figure 5.1- A scanning electron micrograph of a Emiliania huxleyi cell (277)

UVB radiation is the primary source of vitamin D for humans, whether endogenously synthesized or what little is consumed from animal or fungal dietary sources. Vitamin D has been shown to be beneficial to respiratory health. Supplementation has been shown to reduce rates of viral infections and asthma exacerbations in inhaled corticosteroid (ICS)-controlled patients (116) (191). Conversely, vitamin D deficiency is associated with higher susceptibility to LRTI and acute asthma exacerbation (129) (211) (212).

This chapter will further analyse the influence environmental factors which affect paediatric asthma admissions on a population level, building on the findings from the Davies *et al* confirmatory analysis in Chapter 2 (143). Summaries of asthma epidemiology, pathophysiology and the theoretical mechanisms of action of vitamin D are included in chapters 1 and 2. The effect of factors such as deprivation and smoking on the potential relationship between asthma admissions and UVB levels will also be explored, as they have both been independently linked to poor asthma outcomes in children (213) (214) (215).

5.2 Methods

Admissions data were obtained through an NHS hospital episode statistics (HES) dataset. The data described annual raw number of hospital admissions of children aged under 14 years old with asthma from each GP practice for 5 years, from 1st April 2013 to 31st March 2018. Asthma was defined using the International Classification of Disease 10th Edition (ICD-10) codes J45 and J46 (asthma and status asthmaticus respectively).

For anonymisation purposes, small numbers (between 1 and 5) were uniformly recorded as 5 admissions, which was changed to 3 as the midpoint of the suppressed range. Using GP practice codes, these admissions data were linked to corresponding practice names and postcodes, clinical commissioning group (CCG) names and codes, commissioning region names and codes and higher-level health group names and codes (HLHG). NHS prescription service datasets were used to link the HES admissions data to their corresponding practice data (216).

GP practice population data were used to calculate crude asthma admission rates per 100,000 per annum, using NHS Digital datasets showing practice age demographics for April of each year (2013-2018) (217). In these datasets, numbers of male and female children in each practice were shown in age groups from 0-4, 5-9 and 10-14 years old. Age and gender variables were created to indirectly control for these population demographics as covariates in the statistical models. Acute asthma admission rates per 100,000 per annum were calculated by dividing the admissions figure for each practice, dividing it by the total child population (from 0 to 14 years old) of each practice then multiplying this by 100,000.

Each practice had latitude and longitude variables generated using an online postcode batch converter which uses Office for National Statistics (ONS) data (218). The accuracy of the batch conversion was assessed using a random sampling method, using a sample size determined by the equation shown Equation 1. Latitude and longitude data for 381 postcodes were manually checked using online maps software, using a random number generator to select which of the 7966 postcodes to process (219). Whilst this is a formula to give only a rough estimate of the appropriate sample size for a population and thought to lack mathematical rigour, every latitude and longitude value manually checked matched exactly with the generated values (220).

Equation 1- Slovin's formula for estimating representative sample size

$$n = \frac{N}{1+Ne^2}$$

n=sample size, N=population size, e=significance level

Ultraviolet-B radiation data were obtained through the Tropospheric Emission Monitoring Internet Service (TEMIS), which is provided by the Royal Netherlands Meteorological Institute in conjunction with the European Space Agency (ESA) (221). The TEMIS data uses satellite observations of ozone and cloud cover to elicit UVB levels that reach the Earth's surface, specifically of the wavelengths required to endogenously synthesize vitamin D (290-315nm, controlling for surface altitude and surface albedo (222) (223) (224).

Satellite instruments used for TEMIS data inputs include GOME (Global Ozone Monitoring Experiment), GOME-2, SCIAMACHY (Scanning Imaging Absorption spectrometer for

Figure 5.2- Satellites from which TEMIS data inputs are derived. Upper left: ERS-2 (224), upper right: MetOp-A (225), lower left: Envisat (226), lower right: Sentinel-5P (227).

Atmospheric Chartography) and OMI (Ozone Monitoring Instrument); these instruments are located on the ERS-2, MetOp-A, Envisat and Sentinel-5P satellites (respectively) (Figure 5.2) (225). The TEMIS v2.0 data from which the UVB variables used in this study were derived were recorded from SCIAMACHY/Envisat and GOME-2/MetOp-A instruments (223). These satellites measure atmospheric ozone (O_3) distribution along the successive North-South orbits they follow.

Corresponding UVB values are found using the empirical relationship between ozone concentrations recorded for a geographical area and the position of the sun above the horizon (the solar zenith angle, SZA) (223) (226). Using this function, daily UV Index (UVI) in Watts/m^2 for the vitamin D-specific action spectrum is calculated from a total of recordings taken at 5-minute intervals, using the SZA at each time step (t). Cumulative vitamin D-UVB values derived are then correction for factors expressed in Equation 2. Corrections are made for attenuating factors such as cloud cover (f_C), as well as surface elevation (f_H), surface albedo (reflectivity of ground surface) (f_A) and variations in Sun-Earth distance (f_D).

Equation 2- TEMIS parameterisation equation describing UV level derivation from satellite O_3 concentration recordings (223).

$$UVI(t) = UVI' \cdot f_D \cdot f_C \cdot f_H \cdot f_A \qquad (Wm^{-2})$$

The cloud-correction factor is generated using meteorological data collected by the Spinning Enhanced Visible and Infrared Imager (SEVIRI) located on the Meteosat Second Generation (MSG) satellite (Figure 5.3) (223).

Two variables from TEMIS data were used in the analyses in this chapter: cloud-free vitamin D UVB (D-UVB), describing annual UVB levels uncorrected for cloud cover; and cloud-modified D-UVB, which controls for attenuation and represents more accurately the yearly total vitamin D-specific UVB radiation able to reach the skin of the paediatric population of England. The spatial resolution of the TEMIS D-UVB data is in 0.25 x 0.25 degree (~27km) square blocks. Latitude and longitude data for each GP practice were used to match admissions data with TEMIS UVB data regions.

Figure 5.3- The Meteosat satellite being weighed before launch (288).

Socioeconomic deprivation was included as a covariate in the model. Income Deprivation Affecting Children Index (IDACI) scores from 2015 were found for each GP practice postcode, using a batch generator on a government website for the Ministry of Housing, Communities and Local Government (227). Smoking rates were also controlled for by using the percentage of mothers smoking at the time of delivery (SATOD). This was taken from an NHS Digital dataset describing new mothers' smoking statuses on a CCG level; each practice was matched to its respective CCG to create the smoking covariate included in the model (228).

Two multivariate linear regression analyses were carried out to explore the effect of firstly cloud-free D-UVB and secondly cloud-modified D-UVB on acute paediatric asthma admissions. In both statistical models, the following covariates were included for each GP

practice: age, gender, latitude and longitude, IDACI score and the percentage of mothers SATOD.

The GP practice-level data were then sorted by their corresponding Clinical Commissioning Groups (CCG), then for each variable included in the model- admission rates, UVB levels, latitude et cetera- an average was made including all GP practices within each CCG. This manipulation of the data gave a new dataset of 209 CCG-level observations. The linear regression analyses carried out for practice-level data were repeated with CCG-level data, again looking for significant associations between acute paediatric asthma admission rates and both cloud-free and cloud-modified D-UVB levels. All analyses were performed using STATA version 8.0 (STATA Corp, Texas, USA).

5.3 Results

Data on child admission rates on GP practice level showed that in the period between April 1st 2013 and March 31st 2018, 137,164 children under 14 were admitted acutely to hospital with asthma, with an average of 27,433 admissions annually. The child population in this period ranged from 9,649,585 in 2013/14 to 10,118,612 in 2017/18, steadily increasing by an average of 117,257 each year. The average asthma admission rate from 2013-2018 was 314 per 100,000 per annum; the year with the lowest average admission rate was 2017 which saw 287 per 100,000 children admitted to hospital with asthma per annum. The highest annual average admission rate found was 336 per 100,000 per annum in 2014. The average asthma admission rate on the larger aggregate data level of CCG was 334 per 100,000 per

annum, annual average admission rates ranged from 288 per 100,000 per annum in 2017/18 to 416 per 100,000 per annum in 2013/14.

The average UVB levels for all English GP practices between 2013 and 2018 was 1051.78kJ/m^2, uncorrected for climatological factors. When cloud cover, surface albedo and altitude are corrected for, this value is reduced to 794.98 kJ/m^2. Figure 5.5 shows the distribution of cloud-modified UVB recorded by TEMIS, with the Southwest, East Anglia, Southeast and Central regions receiving distinctly more D-UVB than the rest of England. Figure 5.4 illustrates the attenuating effect of cloud cover on surface D-UVB levels by calculating the relative difference between cloud-free and cloud-modified D-UVB levels for each grid cell. The Northeast and particularly the Northwest regions of England appear to be particularly affected by cloud cover. TEMIS data on seasonal D-UVB levels were included in the dataset but not the statistical models. As summarised in Figure 5.6 and Figure 5.7, most D-UVB available to populations of English GP practices was provided in spring and summer months. Figure 5.8 shows the negative correlation between D-UVB exposures and asthma admission rates on a CCG level.

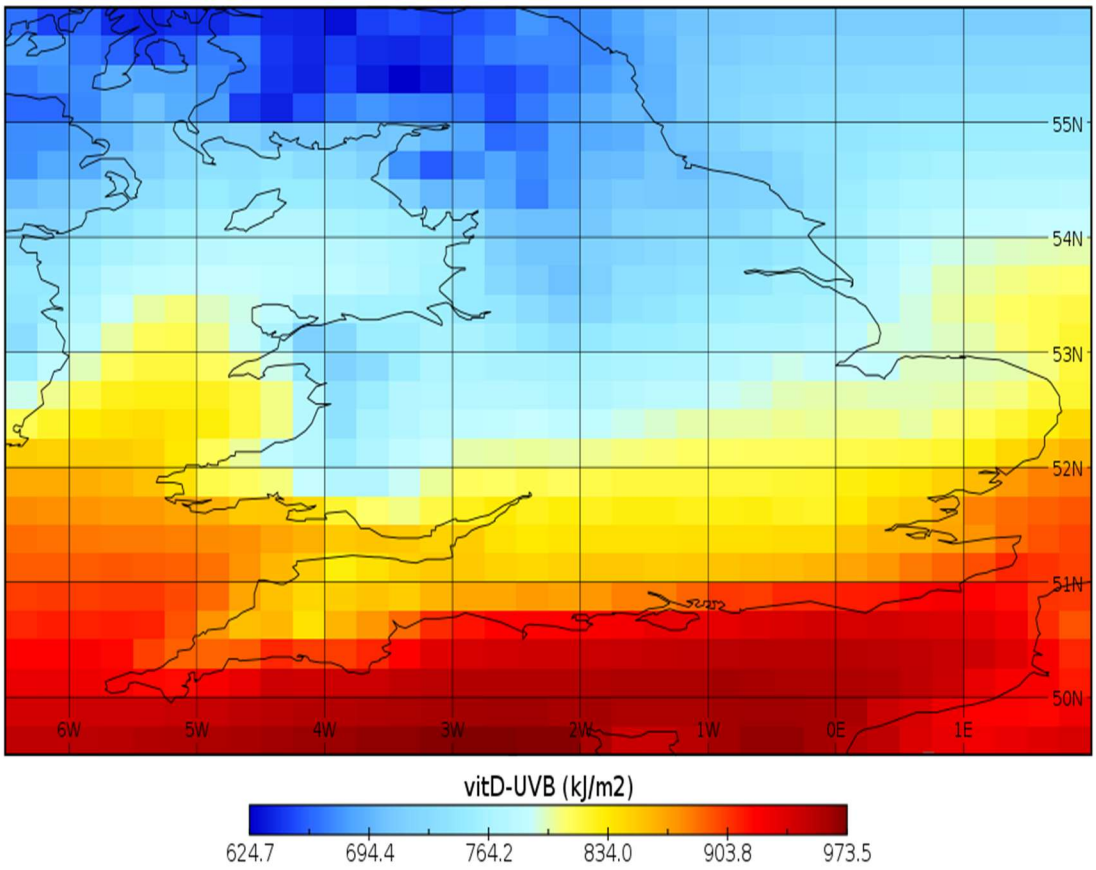

Figure 5.5- Heat map showing levels of total UVB radiation (kJ/m^2) of the vitamin D action spectrum, corrected for cloud cover, an average of yearly totals in England between 2013-2018.

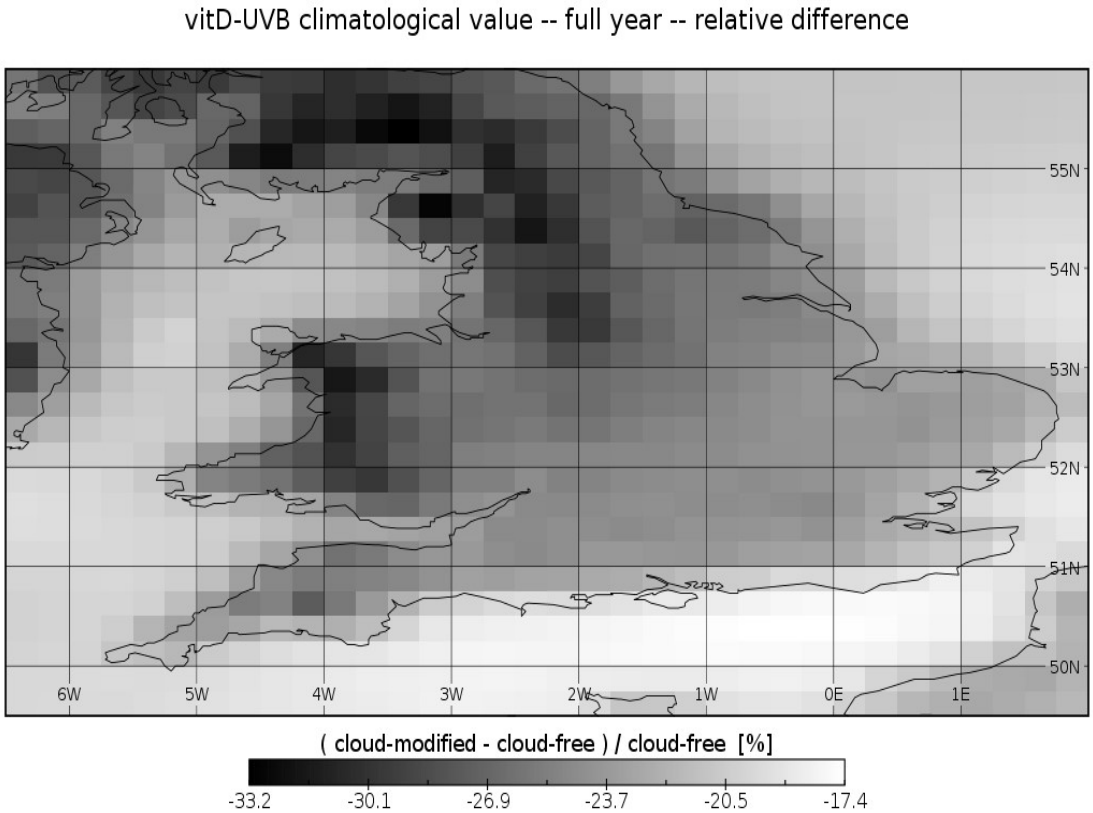

Figure 5.4- A map showing the distribution of the effects of cloud cover, surface albedo and altitude on surface D-UVB levels

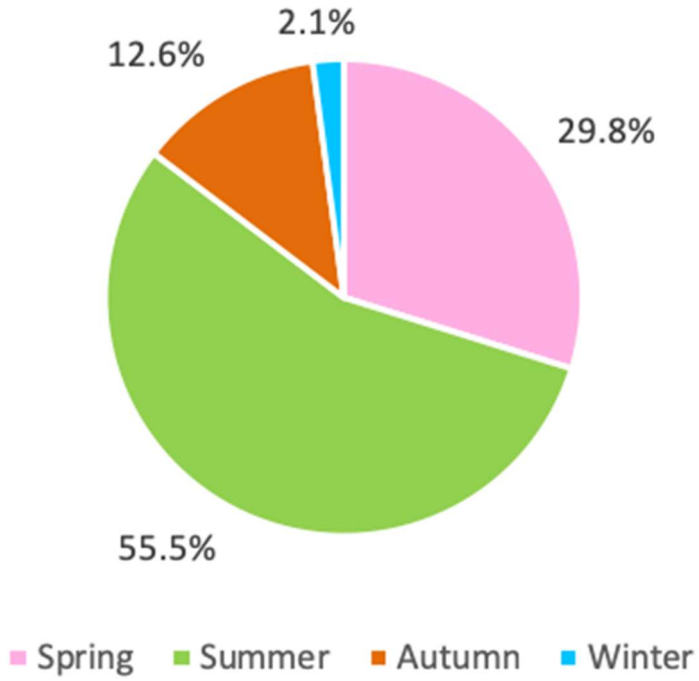

Figure 5.6- A pie chart showing seasonal proportions of D-UVB exposure contributing to annual totals 2013-2018

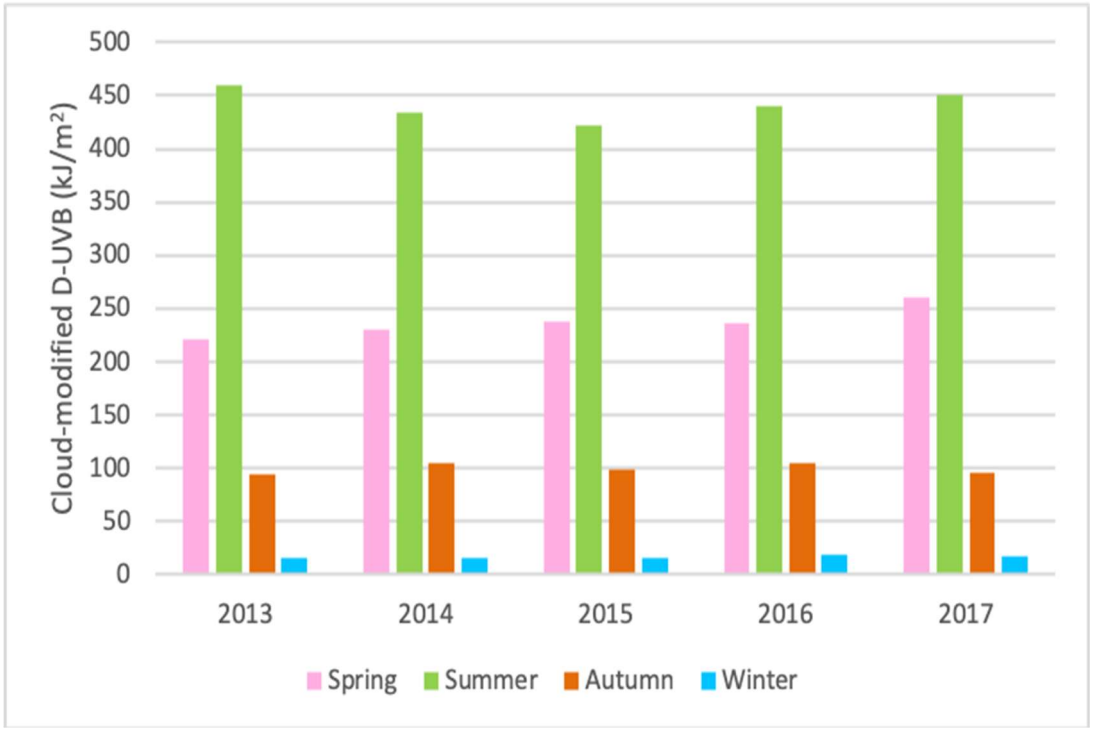

Figure 5.7- A bar chart showing the yearly seasonal average D-UVB levels across England 2013-2018

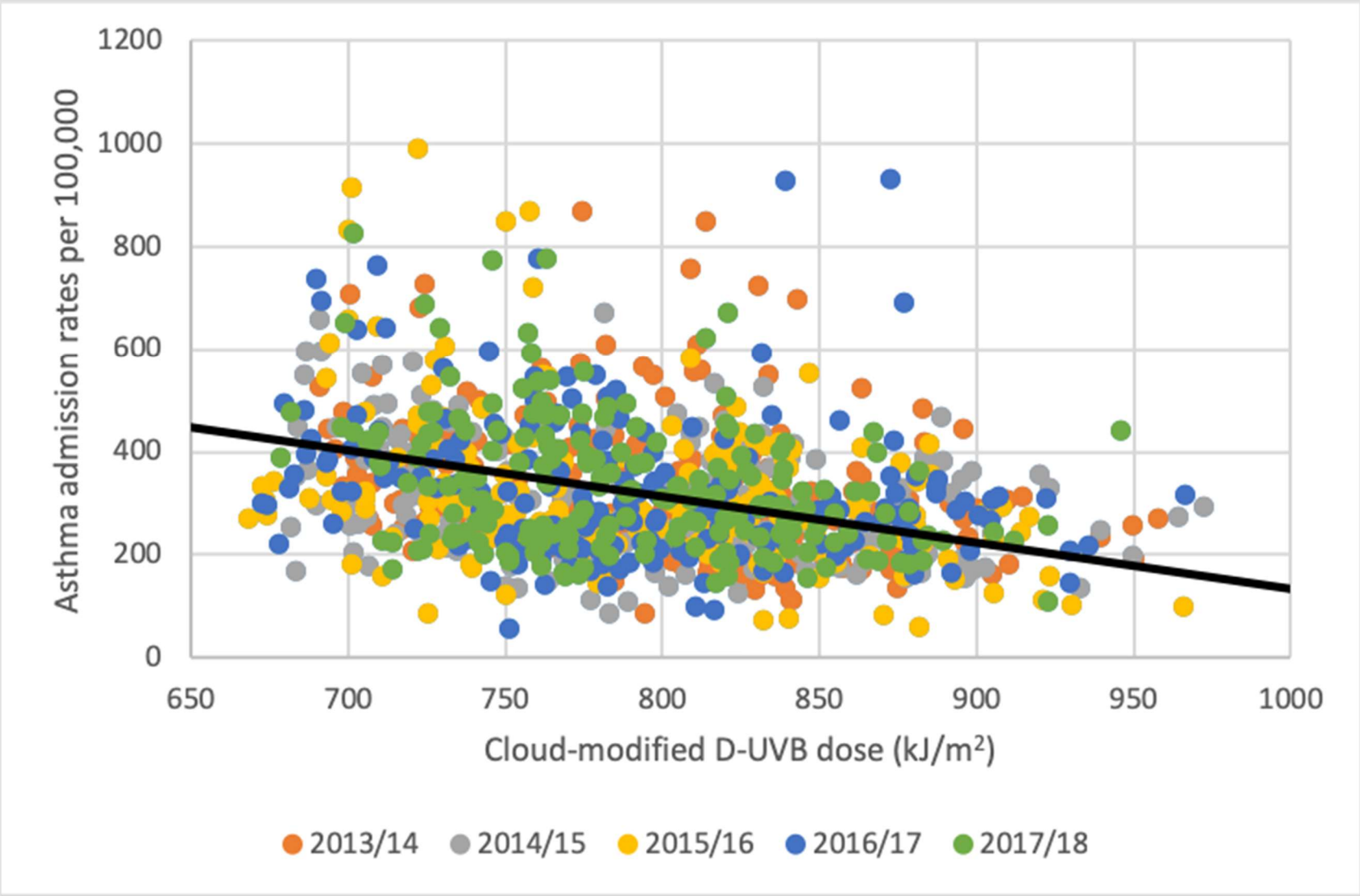

Figure 5.8- A scatter graph showing asthma admission rates to hospital and cloud-modified UVB at a CCG aggregate level.

The results from the linear regression analyses are shown in Tables 5.1-5.4. Cloud-free and cloud-modified D-UVB levels were found to be significantly associated with acute asthma admission rates in children under 14 years old. GP practice age and gender variables, latitude, longitude, IDACI and smoking did not significantly confound this relationship. Socioeconomic deprivation was significantly associated with asthma admission rates, however maternal smoking as a determinant of population asthma admission rates became insignificant when the D-UVB variable was corrected for cloud cover (Table 5.3).

Correcting for cloud cover, surface albedo and altitude led to an increase in the adjusted R^2 (variance) when carrying out the regression analyses (an increase from 0.013 to 0.0148). Similarly, the regression coefficient in the analysis using cloud-modified D-UVB (-0.945) was larger than the coefficient generated using cloud-free D-UVB data (-0.379).

Although the statistical significance of several individual variables in our regression model remained high with p values of <0.001 seen for D-UVB, gender, location, IDACI, and maternal smoking in pregnancy the estimated variance for this model was low. The variance given by the results of the multivariate linear regression analysis using cloud-modified D-UVB data was only 0.0148.

The net effect of variation in D-UVB is also relatively small. This analysis describes how if a GP practice is exposed to an increase in total annual D-UVB levels by 100kJ/m^2, this associates with a reduction in the rate of children admitted to hospital with asthma from that practice population of 94.5 per 100,000 per annum. Furthermore, a 0.1 increase in a GP

practice's postcode-derived IDACI score is associated with a reduction in asthma admissions in children from that practice of 223 per 100,000 per annum.

Table 5.1- GP-level univariate linear regression analyses of the association between asthma admission rates per 100,000 per annum and D-UVB

	Asthma admission rate per 100,000 per annum				
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**	***Adjusted R^2 (variance)***
Cloud free D-UVB	-0.663	-0.741, -0.584	<0.001	-16.5	0.0071
Cloud modified D-UVB	-0.735	-0.811, -0.6590	<0.001	-10.0	-.0095

Table 5.2- Results from the analysis of GP-level emergency asthma admission rates per 100,000 in English children <14 years old per annum and cloud-free D-UVB.

	Asthma admission rate per 100,000 per annum			
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**
Cloud free D-UVB	-0.379	-0.550, -0.208	<0.001	-4.34
Age	10.7	-0.541, 21.9	0.062	1.87
Gender	-3.90	-6.40, -1.40	<0.001	-3.05
Latitude	11.4	2.01, 20.7	0.017	2.38
Longitude	-14.1	-18.2, -9.99	<0.001	-6.73
IDACI	230	194, 265	<0.001	12.63
Maternal smoking	-1.71	-2.96, -0.455	<0.001	-2.67

Adjusted R^2 (variance) = 0.0130

Table 5.3- Results from the analysis of GP-level emergency asthma admission rates per 100,000 in English children <14 years old per annum and cloud-modified D-UVB.

	Asthma admission rate per 100,000 per annum			
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**
Cloud modified D-UVB	-0.945	-1.14, -0.747	<0.001	-9.36
Age	14.4	3.15, 25.6	0.012	2.51
Gender	-4.10	-6.60, -1.61	<0.001	-3.22
Latitude	-20.7	-32.2, -9.17	<0.001	-3.52
Longitude	-12.5	-16.6, -8.36	<0.001	-5.95
IDACI	224	189, 260	<0.001	12.34
Maternal smoking	-0.27	-1.56, 1.02	0.679	-0.41

Adjusted R^2 (variance) = 0.0148

The results from the multivariate regression analyses using CCG aggregate data also show asthma admission rates are significantly associated with cloud-free and cloud-modified D-UVB levels (Table 5.3 and Table 5.6). Likewise, the magnitude of the regression coefficients increases from -0.844 in the cloud-free D-UVB analysis, to -2.10 when using cloud-modified D-UVB data. The CCG-level analyses gave adjusted R^2 values of 0.2144 (cloud-free) and 0.3069 (cloud-modified). The results in Table 5.6 show that an increase in total annual D-UVB exposure by 100kJ/m^2 the CCG region associates with a reduced asthma admission rate by 210 per 100,000 per annum, a reduction of 62.9% relative to the mean CCG rate. The adjusted R^2 value found in this analysis (0.3069) shows that 30.69% of the variation in asthma admission rates is determined by the variables included in this model. IDACI score remained a significant covariate in this model, a 0.1 increase in IDACI score is associated with an increase in asthma admission rate of 650 per 100,000 per annum. Relative to the average CCG rate, this is a 195% increase. No significant relationship was found between CCG maternal smoking rates and asthma admission rates (Table 5.6).

Table 5.4- CCG-level univariate linear regression analyses of the association between asthma admission rates per 100,000 per annum and D-UVB

	Asthma admission rate per 100,000 per annum				
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**	***Adjusted R^2 (variance)***
Cloud free D-UVB	-0.743	-0.887, -0.598	<0.001	-10.1	0.0760
Cloud modified D-UVB	-0.942	-1.07 -0.815	<0.001	-14.5	0.146

Table 5.5- Results from the analysis of CCG-level emergency asthma admission rates per 100,000 in English children <14 years old per annum and cloud-free D-UVB.

	Asthma admission rate per 100,000 per annum			
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**
Cloud free D-UVB	-0.844	-1.16, -0.526	<0.001	-5.21
Age	-141	-192, -89.3	<0.001	-5.37
Gender	-7.99	-11.8, -4.20	<0.001	-4.14
Latitude	-18.1	-35.4, -0.791	0.04	-2.05
Longitude	-21.4	-28.7, -14.2	<0.001	-5.79
IDACI	514	361, 668	<0.001	6.58
Maternal smoking	-0.929	-2.96, 1.11	0.370	-5.81

Adjusted R^2 (variance) = 0.2144

Table 5.6- Results from the analysis of CCG-level emergency asthma admissions to hospital per 100,000 in English children <14 years old per annum and cloud-modified D-UVB.

	Asthma admission rate per 100,000 per annum			
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**
Cloud modified D-UVB	-2.10	-2.40, -1.80	<0.001	-13.9
Age	-17.0	-68.5, 34.5	0.518	-0.65
Gender	-6.21	-9.78, -2.64	<0.001	-3.41
Latitude	-87.8	-105, -70.3	<0.001	-9.85
Longitude	-8.63	-15.7, -1.57	0.017	-2.40
IDACI	650	506, 795	<0.001	0.85
Maternal smoking	0.832	-1.08, 2.74	0.394	8.82

Adjusted R^2 (variance) = 0.3069

5.4 Discussion

These analyses have exhibited a statistically strong and significant relationship between vitamin D-producing UVB radiation and acute paediatric asthma admission rates at both GP and CCG levels. There is supporting evidence from existing literature to link UVB radiation, particularly of the wavelengths for efficient vitamin D production used in this analysis, to population serum 25-hydroxyvitamin D levels (73) (229). The UK population relies heavily on UVB radiation from the sun to endogenously synthesize adequate levels of vitamin D, as dietary sources are able to contribute very little to vitamin D status (94). The findings from the analyses in this chapter therefore provides evidence to support the argument that asthma rates in children could be influenced by vitamin D status, which is determined principally by environmental factors. This effect is biologically plausible, with potential immunological mechanisms identified and the effect of vitamin D deficiency on poor asthma outcomes well-documented (129) (230).

The significance of associations and explanatory capacity of the models found in both GP and CCG level analyses are strengthened when cloud-modified D-UVB is analysed. This shows that climatological factors interact with the ability of child populations to synthesize vitamin D from UVB radiation, attenuating the intensity of the UVB in areas with more cloud cover (Figure 5.4). UVB levels in northwest areas in England were especially attenuated by cloud cover; this effect became less pronounced further east, perhaps explaining why longitude was significantly associated with lower asthma admissions in all four analyses. A limitation of the analyses in this chapter is that no other climate variables were included in the linear regression models. Total annual hours of sunlight, rainfall and average air

temperature could give more detail when assessing the environmental factors impacting population vitamin D status and asthma admission rates.

Second hand smoke exposure, considered a predictor of childhood asthma, were not significantly associated with admission rates in the models using cloud-modified D-UVB data (214). A crude univariate analysis of socioeconomic deprivation and smoking variables from the CCG-level dataset showed that the two variables are positively correlated. An explanation of the insignificance of smoking within the model could be that the NHS Digital dataset on CCG-level maternal smoking rates at the time of delivery gives poor indirect markers of individual environmental tobacco exposure. Data describing GP practice smoking rates were unavailable, however future analyses could include CCG data on smoking rates more generally in the population.

Socioeconomic deprivation was a significant, potent determinant of child asthma exacerbations in all four analyses carried out. There is a myriad of factors linked to deprivation that could explain this relationship; these include exposure to pollution and allergens, ethnicity, exposure to psychological stress, tobacco smoke exposure, and access to healthcare (215). Pollution is a measurable environmental factor regularly associated with deprivation that has been shown to negatively impact respiratory health (231) (232). Postcode or CCG level data on airborne pollutants such as nitrogen dioxide (NO_2) or particulate matter ($PM_{2.5}$) known to impact asthma and respiratory health in children could be used to control for these effects on asthma admission rates (232).

Rurality and the more primary care-orientated management of asthma that comes with it could, as discussed in Chapter 2, lead to an underestimation of asthma control in more rural areas. Indices of rurality could be controlled for in future studies, as it may improve the model by controlling for this potential confounder.

5.4.1 Strengths and limitations

Small number suppression is a major limitation in using the HES dataset for 2013-2018 asthma admissions in this chapter's analyses. Anonymisation concerns meant that any GP practice which saw between 1 and 5 children from its population admitted to A&E was automatically recorded as a 5 in the HES database, converted in this study to 3.

Table 5.7 shows that 82.6% of the asthma data used in these analyses was essentially binary. When converted to admission rates using 0 to 14-year-old practice populations, upon inspection the data appeared more diverse. Nevertheless, small number suppression is a major flaw in the source data, which could potentially explain the relatively low adjusted R^2 values found in the GP level analyses.

Table 5.7- A table showing the extent of small number suppression in the HES dataset on acute paediatric asthma admissions by showing numbers and proportions of datapoints suppressed each year (GP level).

	2013-14	2014-15	2015-16	2016-17	2017-18	Average
0	1757	1700	1866	1869	2198	1878
>5	1258	1517	1403	1463	1297	1387.6
5	4951	4749	4697	4634	4471	4700.4
Total	7966	7966	7966	7966	7966	7966
%: 0	22.1%	21.3%	23.4%	23.5%	27.6%	23.6%
%: 5	62.2%	59.6%	59.0%	58.2%	56.1%	59.0%
%: 0 or 5	84.2%	81.0%	82.4%	81.6%	83.7%	82.6%

There is a dramatic increase in adjusted R^2 values found when running linear regression analyses using variables generated from practice data grouped by CCG from the same dataset (0.0148 to 0.3069, cloud-modified D-UVB analyses). By dividing the average CCG-level asthma admission rate for 2013/14, 395.35 per 100,000, by the average admission rate given for England in 2010/11 by the HES dataset used in Chapter 2, 232.94 per 100,000 (free from anonymization measures), it can be estimated that small number suppression could contribute to an overestimation of asthma admission rates by a factor of 1.70. This is assuming there is no dramatic change in the average admission rate for England between 2010 and 2013. This is certainly a source of error in these analyses, due to the relative reduction in precision of the data.

The explanatory capacity of this model increases by a factor of 20 by examining the same relationships from a larger aggregate level. This could be due to the mitigation of the effect small number suppression has on the data; averages of similar practice data could be reducing over- or under-estimations of child asthma admission rates. Another reason for this improvement in variance is that the CCG-level analyses circumvented the impact of 'zero inflation' on the effects found using the original GP-level data. As show in Table 5.7, 23.6% of

the HES data were recorded as '0'. Data with excess zero counts are often highly dispersed and positively skewed (233). The generated CCG aggregate data, without excess zero counts, could have attenuated the effects of zero inflation and, upon analysis, given the drastically higher adjusted R^2 values than the GP-level data. Future research using the same or similar data of this scale could use zero-inflated Poisson (ZIP) regression.

In any case, the results from this chapter suggest that CCG aggregate size may provide a more appropriate level of granularity with which to explore associations in these statistical models. If this study were to be repeated, it would be more astute to collect paediatric asthma admission rate data from CCGs themselves instead of forming new variables from grouped practice averages. Another benefit of using data at this scale is that age and gender correction could be included as a part of the admission rate variable, avoiding the need to create age and gender variables to include in analysis.

A major strength of this study is the reliability of the TEMIS data on D-UVB levels. Its satellite data on annual estimated surface UVB exposures is synoptically collected throughout the year, with the derivation of vitamin D-spectrum UVB radiation from recorded atmospheric ozone levels and distribution being previously validated, accurately estimating UVB levels which correspond with ground-level recordings (223). As discussed in the methods section of this chapter, the process to calculate D-UVB levels uses the solar zenith angle (SZA) to account for the angle at which UV rays travel through Earth's atmosphere. A more oblique SZA and the heightened UVB attenuation that follows is the cause behind reduced vitamin D synthesis at higher latitudes. Latitude and its association with lower asthma admissions is significant in the results of three of four analyses in this chapter.

The D-UVB variables themselves inherently account for the influence of latitude on potential population vitamin D status, therefore there must be another explanation behind this effect. Whilst this result does not contradict the understanding from previous research that latitude negatively impacts asthma admission rates (cloud-modified UVB, corrected for SZA attenuation), a positive latitudinal impact on asthma admissions has been independently identified (234).

There is further potential for TEMIS UVB data to be used to explore the relationship between asthma admission rates and vitamin D status, as seasonal totals have also been recorded in this dataset. Future research could explore the difference made nationally to paediatric asthma admissions by UVB levels of varying intensities at different times of the year. While annualization was controlled for in these analyses, it would be illuminating to investigate the presence of a cyclical relationship between asthma admissions and UVB across the year.

A limitation of the data used to analyse associations between asthma admissions and D-UVB levels is that while HES admissions data describes children's admission to hospital starting in April and finishing in March each year, the annual UVB data provides information on the opportunity for the child population to synthesize vitamin D starting in January each year. The inability to match these variables to each other accurately could influence the results of the analyses. However, the 3-month period (January 1st to April 1st) during which the data is mismatched is a period when very little vitamin D can be synthesized relative to summer

(73). This was a flaw difficult to avoid in this study, however, the error potentially introduced is unlikely to significantly impact the proxy exploration of annual vitamin D status.

5.4.2 Implications for clinical practice

The findings of the work detailed in this chapter serve to remind clinicians that the environment from which patients admitted to hospital come from has a significant influence on their health. Whether managing asthma in primary care or in hospital clinics, an awareness of the increased risk posed to children of asthma exacerbation in areas with low annual UVB exposure or higher socioeconomic deprivation would equip a clinician to treat the patients they see more holistically. Similarly, an awareness of the factors that predispose children to vitamin D deficiency- not just geographical UVB exposures, but pollution, ethnicity, behaviour and a lack of supplementation- may help to identify children who are more susceptible to acute asthma exacerbations. Stronger advocacy of national vitamin D supplementation should complement the recommendation of taking vitamin D individually and the encouragement of judicial sun exposure in children at risk of vitamin D deficiency. The findings of this study suggest that asthma control suffers in the absence of sufficient D-UVB availability, therefore ensuring children's access to alternate, reliable sources of vitamin D in geographical areas could improve health outcomes on a population level.

5.5 Summary

In this chapter, annual UVB radiation levels, of wavelengths specific to the vitamin D action spectrum, were found to be significantly associated with acute asthma admissions in English children in real and relative terms. The associations found were stronger both when analysis involved data at a CCG aggregate level, and when cloud-corrected D-UVB variables were

used. Socioeconomic deprivation was found to significantly affect child asthma control in all analyses carried out, and factors such as pollution associated with poor vitamin D status, deprivation and respiratory health could be useful to include in similar models in the future. Chapter 6 will follow the methodology implemented in this chapter, building on the regional findings from Chapter 3 by examining the relationship between D-UVB levels and lower respiratory tract infection rates.

6 Ultraviolet-B Radiation and lower respiratory tract infection

6.1 Introduction

Viruses and vitamins have an extensive relationship in the human body. Casimir Funk, a Polish biochemist, is credited with first describing 'vital amines' or vitamins as they became known (235). Vitamin D is not the first vitamin to be associated with immune function. Vitamin A was discovered alongside vitamin D, in an attempt to find a dietary agent to prevent rickets, an endemic disease pervasively affecting the British population in the early 20th century (236). Cells of the immune system, such as alveolar macrophages, express enzymes to convert retinoic acid (vitamin A) into its active metabolite (237). This has been found to be integral in dendritic cell differentiation and encourages polarisation of regulatory T-cell phenotypes (237).

Vitamin C has a key role in efficient anti-viral defence; it accumulates in phagocytes, enhancing responses by augmenting chemotaxis and regulating reactive oxygen species production (238). Vitamin C deficiency leads to poor wound healing and impaired immune function; severe deficiency manifests as the scurvy, which frequently culminates in potentially fatal pneumonia if untreated (239). Vitamins A and C are only obtained through dietary sources, and while uncommon to see deficiency in the UK, both are serious global health concerns (240). Vitamin D deficiency is widespread in the UK (54). Maintaining an adequate vitamin D status only relies completely on dietary consumption when there is no skin exposure to ultraviolet radiation. Consequently, pathologies which are more likely to manifest in vitamin D-deficient individuals would theoretically be more susceptible to

changes in the environment which influence the availability of adequate UVB radiation to a population.

In this chapter, the relationship between lower respiratory tract infection (LRTI) admission rates in English children and UVB levels will be explored. Methods used in Chapter 5 will be followed. Topics including the prevalence of LRTI in children and the anti-viral physiology of vitamin D are covered in chapters 1 and 3. The effects of other potential determinants of poor respiratory health outcomes in a child's environment such as smoking rates and socioeconomic deprivation will also be investigated.

6.2 Methods

Hospital episode statistics (HES) data were used to create a variable describing acute LRTI admission rates in English children under 14 years old. The study period was during the three financial years between 2016/17 and 2018/19. The dataset showed individual GP practices and the number of children admitted to hospital with LRTI from each practice. Admissions were recorded in the dataset as being caused by LRTI according to ICD-10 codes (Table 6.1).

Observations recorded as less than 7 were coded as '7' for anonymization purposes, with any number above 7 rounded to the nearest 5. Each value of 7 was changed to 4 in the dataset, as the midpoint between 1 and 7. Practice postcode, corresponding Clinical Commissioning Group (CCG) name and code, higher-level health group (HLHG) names and codes were found using NHS Prescription Service datasets (216). These admissions numbers were converted to crude LRTI admission rates for each GP practice. To do this, GP practice population data (which includes how many male and female children there are in age groups

Table 6.1- ICD-10 codes used to record LRTI admissions in this HES dataset and their corresponding conditions

ICD-10 Code	Condition coded for on admission
J10.0	Influenza with pneumonia, other influenza virus identified
J11.0	Influenza with pneumonia virus not identified
J11.1	Influenza with other respiratory manifestations virus not identified
J12	Viral pneumonia not elsewhere classified
J13	Pneumonia due to *Streptococcus pneumoniae*
J14	Pneumonia due to *Haemophilus influenzae*
J15	Bacterial pneumonia not elsewhere classified
J16.0	Chlamydial pneumonia
J18.0	Bronchopneumonia unspecified
J18.1	Lobar pneumonia unspecified
J18.9	Pneumonia unspecified
J21	Acute bronchiolitis

(0-4, 5-9 and 10-14) was used to divide the corresponding practice LRTI admission numbers by the total child population (aged 0-14), then multiplying this by 100,000The age and gender breakdown for each practice was used to calculate age and gender variables to include in the model to control for these factors.

Latitude and longitude data for each practice was required to link the admissions and D-UVB data. This geographical data were obtained by using an online batch converter to acquire the latitude and longitude of GP practices based on their postcode (218). Office for National Statistics (ONS) data is the converter's source, and random sampling was used to manually verify the latitude and longitude data to further guarantee the accuracy of the batch conversion (219). A crude sample size of 370 was determined for this process by using Slovin's formula (Equation 1), and a random number generator was used to select which of

Equation 3- Slovin's formula for estimating representative sample size

$$n = \frac{N}{1+Ne^2}$$

n=sample size, N=population size, e=significance level

the 7789 postcodes to manually check. Not one postcode manually checked had latitudes and longitudes different to that of the automatically converted values.

Ultraviolet-B (UVB) radiation data were obtained through the Tropospheric Emission Monitoring Internet Service (TEMIS), whose satellite data products are obtained from European Space Agency satellites (221). Orbiting at around 800km above the GP practices covered in this study, the satellites contributing towards the dataset used are the EnviSat and MetOp-A satellites, using the Scanning Imaging Absorption spectrometer for Atmospheric Chartography (SCIAMACHY) (Figure 6.1) and Global Ozone Monitoring Experiment-2 (GOME-2) (Figure 6.2) instruments (respectively) to measure satmospheric ozone chemistry. The ozone distribution data collected by

Figure 6.1- SCIAMACHY detector module, eight of which constitute part of the instrument on board the Envisat satellite (289).

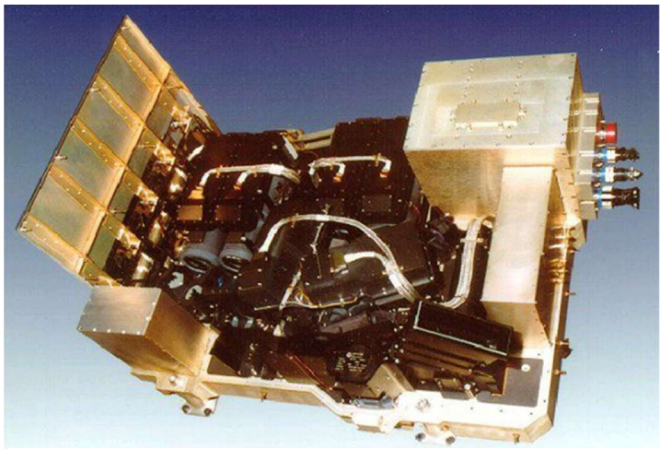

Figure 6.2- The GOME-2 instrument on board the MetOp-A satellite, measuring atmospheric ozone chemistry (244).

these satellite instruments is used to determine the UVB dose (D-UVB), specifically of the wavelengths at which dermal vitamin D synthesis occurs, for geographical areas at a spatial resolution of 0.25 degree square blocks (approximately 27x27km^2) (241).

Generation of D-UVB data is based on a validated empirical relationship between geographic ozone levels and the solar zenith angle (SZA) at that place and time of day (223). Equation 2 is the formula used to complete this process, where D-UVB levels (Watts/m^2) are corrected for variations in Sun-Earth distance (f_D), cloud cover (f_C), surface elevation (f_H) and surface albedo (reflectivity of ground surface) (f_A).

Equation 4- TEMIS parameterisation equation describing UV level derivation from satellite O_3 concentration recordings (223).

$$UVI(t) = UVI' \cdot f_D \cdot f_C \cdot f_H \cdot f_A \qquad (Wm^{-2})$$

The cloud attenuation factor for each UVB recording is determined using satellite meteorological data from the Spinning Enhanced Visible and Infrared Imager (SEVIRI) instrument on the Meteosat Second Generation (MSG) satellite (223). This modified value gives a more accurate representation of how much UVB able to synthesize vitamin D is actually available to a population. The daily cloud-modified D-UVB dose is calculated by recording doses every 5 minutes, factoring in the position of the sun above the horizon (SZA), with the final variables used in this analysis being annual totals for the specified geographical regions.

Both modified and unmodified UVB doses are included as variables in the TEMIS dataset and were used in separate analyses when exploring their effects on paediatric LRTI admission rates. Latitude and longitude values for each GP practice was used to match UVB and admissions data.

Socioeconomic deprivation is a potential confounder of an effect found between environmental factors and LRTI admission rates, therefore Income Deprivation Affecting Children Index (IDACI) scores were included as covariates (242). IDACI scores for 2015 were found for each GP practice by entering all of their corresponding postcodes into a converter on a UK government website (227). Another factor controlled for in this study is smoking rates, another environmental risk factor for children developing LRTI. CCG-level NHS data were found describing the percentage of women smoking at the time of delivery (SATOD) (228). The variable was created by matching GP practices to their respective CCGs and thus their estimated maternal smoking rates.

The GP-level data for LRTI admissions rates, UVB doses, age, gender, latitude and longitude were used to create a second dataset. The practices were grouped into the 201 CCGs they belong to, and averages for each variable were calculated for each group. IDACI and smoking data were primarily CCG-level data, and these were added alongside these CCG averages.

Statistical analysis was carried out using multivariate linear regression for four statistical models. The relationships between LRTI admissions and both cloud-modified and cloud-free D-UVB variables were analysed at both GP and CCG level, alongside covariates of age,

gender, latitude, longitude, IDACI score and %SATOD. These analyses were undertaken using STATA version 8.0 (STATA Corp, Texas, USA).

6.3 Results

In the period between 2016/17 and 2018/19, approximately 233,721 children under 14 were admitted to hospital with LRTI, with an annual average of 77,907 admissions. The child population of the GP practices for which LRTI admission rates were calculated grew from 9,901,567 in 2016/17 to 10,167,204 in 2018/19. The average annual child LRTI admission rate for all years was 678 per 100,000 per annum, ranging from 668 per 100,000 per annum in 2017/18 to 699 per 100,000 per annum in 2016/17. This was reflected in the CCG-level admission rates, with an annual average of 674 per 100,000 per annumfor all years, ranging from an average of 653 per 100,000 per annum in 2017/18 to 697 per 100,000 per annum in 2016/17.

For English GP practices in the HES dataset, the average uncorrected D-UVB exposure between 2016/17 and 2018/19 was 1076kJ/m^2; this reduced to 822.5kJ/m^2 when corrected for cloud cover, surface elevation and albedo. Seasonal D-UVB levels from the same dataset showed that most of the D-UVB available to the child populations in this study was provided in the spring and summer (Figure 6.4 and Figure 6.3).

Figure 6.5 shows the negative correlation observed between acute LRTI admission rates and cloud modified D-UVB. The multivariate linear regression analyses carried out for the GP level data gave results shown in Table 6.3 and Table 6.4. While the association between

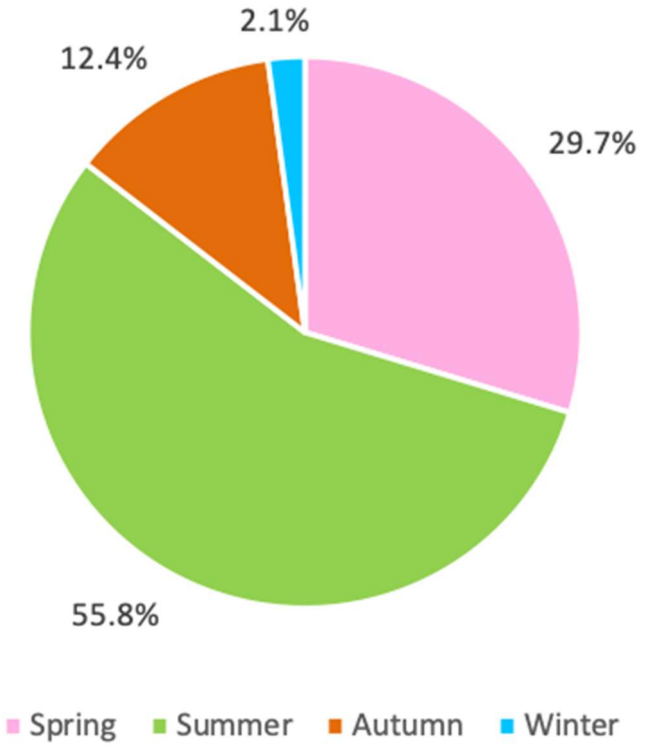

Figure 6.4- A pie chart showing seasonal proportions of D-UVB exposure contributing to annual totals 2016/17-2018/19

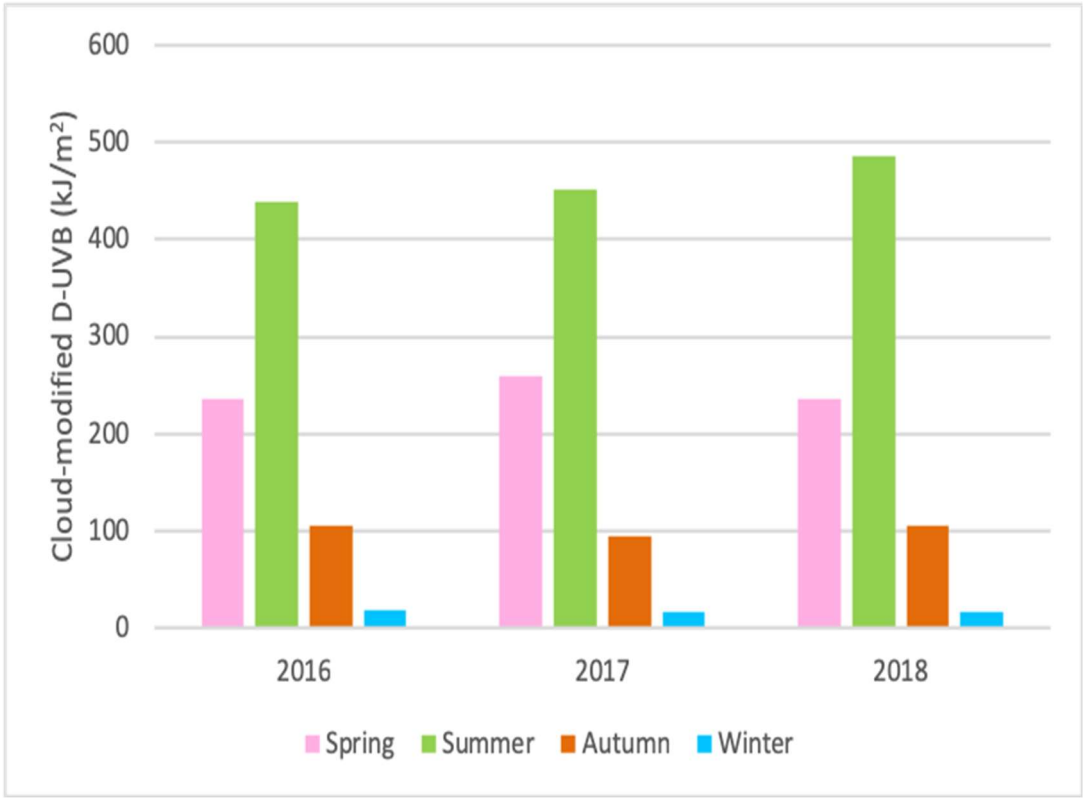

Figure 6.3- A bar chart showing the yearly seasonal average D-UVB levels in England 2016/17-2018/19

climatological attenuation showed a statistically significant relationship with LRTI admissions ($p<0.001$). Covariates including latitude, longitude, IDACI and smoking rates were included in this model; each of these factors was found to be significantly associated with acute paediatric LRTI admissions at a GP aggregate data level.

The explanatory capacity of this multivariate model increased when cloud-modified D-UVB variables were analysed instead of cloud-free D-UVB (an increase in adjusted R^2 value from 0.0605 to 0.0688). The adjusted R^2 value for the linear regression model shown in Table 6.4 is 0.0688, meaning that 6.88% of the variation in LRTI admission rates can be explained by the effects of the other variables. This analysis also showed that GP practices exposed to an additional 100kJ/m^2 in annual D-UVB levels is associated with a reduction in acute LRTI admissions of 172 per 100,000 per annum in its child population.

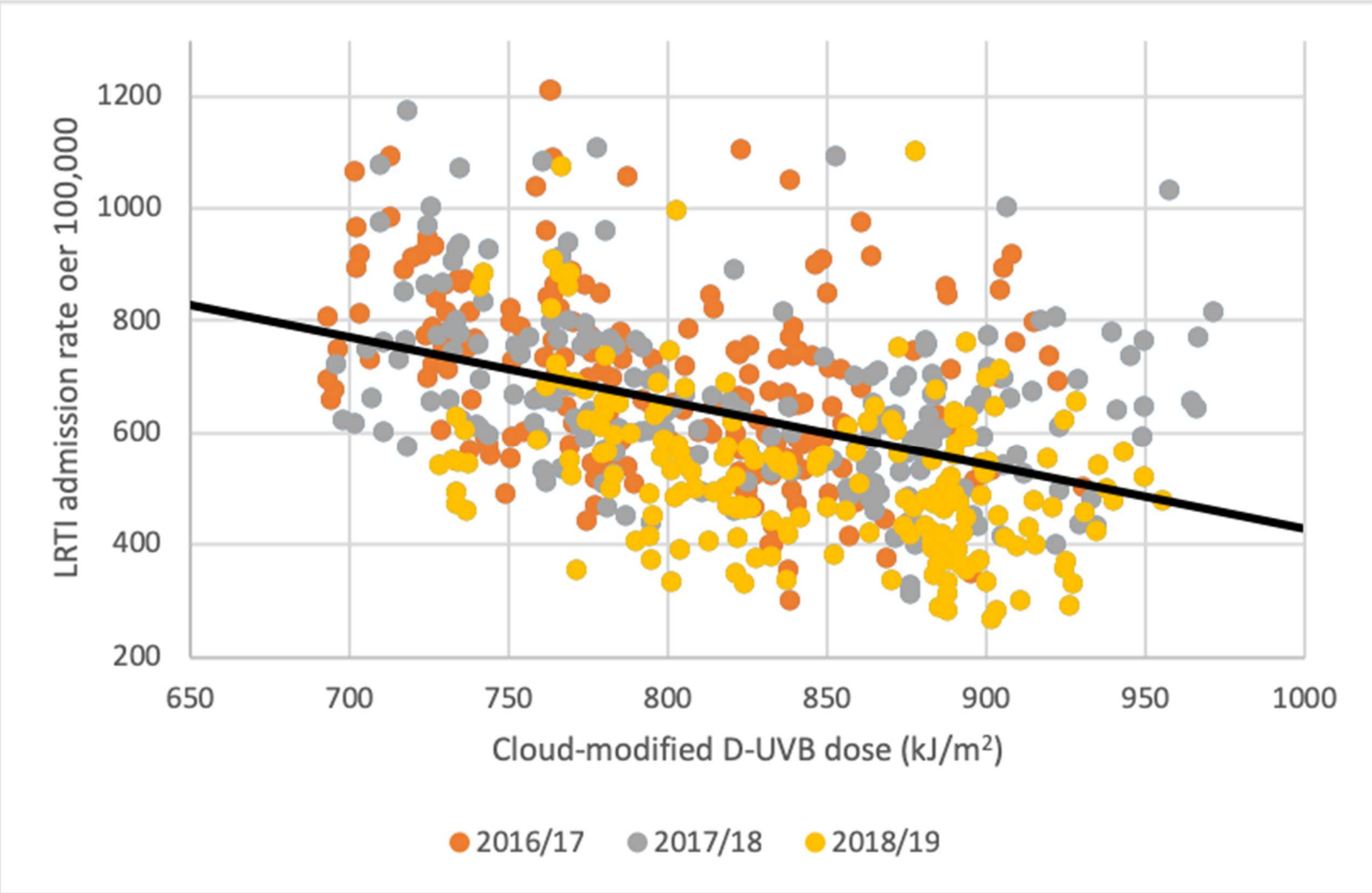

Figure 6.5- A scatter graph showing LRTI admission rates to hospital and cloud-modified UVB at a CCG aggregate level from 2016-2019.

The results also show that a 0.1 increase in a GP practice's postcode-derived IDACI score associates with an increase in LRTI admissions of 293 per 100,000 per annum. It has also been found that a 10% increase in mothers smoking at the time of delivery in a CCG associates with an increase in LRTI admission rates of 63.1 per 100,000 per annum in GP practices in this area.

Table 6.2- GP-level univariate linear regression analyses of the association between LRTI admission rates per 100,000 per annum and D-UVB

	LRTI admission rate per 100,000 per annum				
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**	***Adjusted R^2 (variance)***
Cloud free D-UVB	- 0.784	-0.895, -0.673	<0.001	-13.9	0.0088
Cloud modified D-UVB	-1.04	-1.13, -0.941	<0.001	-21.2	0.0204

Table 6.3- Results from the multivariate linear regression analysis of GP-level emergency LRTI admission rates per 100,000 per annum in English children <14 years old and cloud-free D-UVB

	LRTI admission rate per 100,000 per annum			
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**
Cloud free D-UVB	0.381	-0.175, 7.78	0.061	1.88
Age	-46.2	-62.4, -30.0	<0.001	-5.58
Gender	-9.11	-9.86, -8.36	<0.001	-23.75
Latitude	28.2	8.11, 48.3	<0.001	2.75
Longitude	-43.5	-48.9, -38.1	<0.001	-15.82
IDACI	293	248, 338	<0.001	12.69
Materal smoking	6.31	4.69, 7.87	<0.001	7.64

Adjusted R^2 (variance) = 0.0605

Using the CCG grouped average data, linear regression analyses found cloud-modified D-UVB to be significantly associated with the rate of child admissions to hospital with LRTI ($p<0.001$) (Table 6.7). This was only significant when using the D-UVB corrected for the interfering meteorological factor of cloud cover, cloud-free UVB levels showed no significant relationship with LRTI admissions (Table 6.6)

It was found that every additional 100kJ/m^2 of cloud-modified D-UVB is associated with a reduction in CCG average LRTI admission rates of 208 per 100,000 per annum, a reduction of 30.9% relative to the mean CCG admission rate. A 0.1 increase in the average IDACI score also associates with an increase in acute LRTI admission rates of 500 per 100,000 per annum, an increase of 74.2% relative to the mean.

Table 6.4- Results from the multivariate linear regression analysis of GP-level data on emergency LRTI admission rates per 100,000 per annum in English children <14 years old and cloud-modified D-UVB

	LRTI admission rate per 100,000 per annum			
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**
Cloud modified D-UVB	-1.72	-1.96, -1.48	<0.001	-13.85
Age	-32.1	-48.4, -15.9	<0.001	-3.87
Gender	-8.84	-9.59, -8.09	<0.001	-23.12
Latitude	-79.9	-94.2, -65.6	<0.001	-10.95
Longitude	-30.6	-36.3, -25.0	<0.001	-10.58
IDACI	281	236, 326	<0.001	12.21
Maternal smoking	9.06	7.40, 10.7	<0.001	10.72

Adjusted R^2 (variance) = 0.0688

Smoking was not found to be significantly associated with LRTI admission rates at a CCG level using both cloud-free and cloud-modified D-UVB variables. The adjusted R^2 values (variance) for these CCG level analyses were far higher than for the GP-level analyses. The regression model using cloud-modified D-UVB data accounts for 24.5% of the variation in acute paediatric LRTI admissions.

Table 6.5- CCG-level univariate linear regression analyses of the association between LRTI admission rates per 100,000 per annum and D-UVB

	LRTI admission rate per 100,000 per annum				
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**	***Adjusted R^2 (variance)***
Cloud free D-UVB	-0.982	-1.24, -0.719	<0.001	-7.35	0.0825
Cloud modified D-UVB	-1.18	-1.40, -0.965	<0.001	-10.8	0.1639

Table 6.6- Results from the multivariate linear regression analysis of CCG-level data on emergency LRTI admission rates per 100,000 per annum in English children <14 years old and cloud-free D-UVB

	LRTI admission rate per 100,000 per annum			
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**
Cloud free D-UVB	0.590	-0.446, 1.62	0.264	1.12
Age	-59.5	-168, 49.1	0.283	-1.08
Gender	-14.7	-19.8, -9.66	<0.001	-5.70
Latitude	63.0	11.9, 114	0.016	2.42
Longitude	-35.1	-47.9, -22.4	<0.001	-5.40
IDACI	332	63.3, 600	0.016	2.43
Maternal smoking	1.83	-1.39, 5.05	0.228	1.12

Adjusted R^2 (variance) = 0.1919

Table 6.7- Results from the multivariate linear regression analysis of CCG-level data on emergency LRTI admission rates per 100,000 per annum in English children <14 years old and cloud-modified D-UVB

	LRTI admission rate per 100,000 per annum			
Variable	**Regression coefficient**	**95% Confidence Intervals**	**P value**	**t statistic**
Cloud modified D-UVB	-2.08	-2.72, -1.45	<0.001	-6.47
Age	114	-1.72, 230	0.053	-1.93
Gender	-12.5	-17.4, -7.52	<0.001	-4.95
Latitude	-73.3	-109, -37.5	<0.001	-4.03
Longitude	-17.9	-31.4, -4.53	<0.001	-2.63
IDACI	500	237, 764	<0.001	3.73
Maternal smoking	2.38	-0.732, 5.49	0.134	1.50

Adjusted R^2 (variance) = 0.2450

6.4 Discussion

The analyses in this chapter have demonstrated the presence of an association between acute LRTI admissions in children and D-UVB. This association was only found to be significant at both GP practice and CCG level when the model accounted for attenuating factors that would diminish the dose of UVB radiation before it has the potential to synthesize adequate vitamin D. In addition to the variance, the regression coefficient for cloud-modified D-UVB similarly increased when using data from the larger aggregate data size of CCG, implying that if there is a strong relationship it is best studied at this level.

As discussed in chapter 5, D-UVB recordings are strongly correlated with the vitamin D status of a population which, as is the case in England, heavily relies on endogenous synthesis of vitamin D to maintain sufficient levels to prevent clinical or subclinical pathology (54) (229).

The findings from this chapter therefore add to the evidence-based argument that pathologies such as LRTI are influenced by changes in vitamin D status (118) (116).

Deprivation has previously linked to an increased risk of paediatric acute LRTI (243). The results from the analyses in this chapter reflect this, as all four linear regression models showed IDACI scores to be significantly associated with LRTI admission rates. Both deprivation and child LRTI admission rates are associated with smoking (244). Smoking was found to be significantly associated with LRTI admission rates at a GP practice level, but when using CCG aggregate data, this effect disappeared. This could imply that the effect of smoking rates on child respiratory infection risk could be better observed at a local level, as patterns may be more homogenous at CCG level. However, explanations of this finding are made difficult because the smoking variable itself was created using CCG-level data on maternal smoking patterns which were matched to each GP practice in the first two analyses. It would be useful for similar future research to explore the effects of other factors that are mediated by deprivation on LRTI admissions, such as access to healthcare and pollution (168) (205).

6.4.1 Strengths and limitations

The advantages of using GP-level HES data are the large population size (the average child population in the study period was around 10 million children) and that the data were from small health economies with specific health profiles, therefore making fewer assumptions about the uniformity of the associations found in the population as a whole. However, small number suppression and rounding of admissions numbers limits the utility of this HES dataset. The detail lost due to anonymization of the data could be behind the limited

explanatory capacity, expressed by the low adjusted R^2 values, of the analysis carried out using GP-level data. There is also a likely overestimation in LRTI admission rates that were calculated in this analysis due to small number suppression. The 2016/17 average CCG level LRTI admission rate was 697 per 100,000 per annum, whereas the 2010/11 LRTI admission rate for England (found in the pre-2012 HES dataset used in chapter 3) was 409 per 100,000 per annum. Though the 2016/17 value is a crude, unstandardized rate, the child LRTI admission rate is unlikely to have risen by a factor of 1.7, the exact same proportional increase as was seen in Chapter 5 when estimating the overestimation of HES asthma admission rates due to small number suppression.

As with the data used in Chapter 5, these data are likely affected by 'zero inflation'; more skewed and dispersed data may affect the analyses in this chapter. The impact of this and small number suppression seems to be mitigated in the CCG-level analyses due to the more than three-fold increase in adjusted R^2 values. Using annualised data was also useful to eliminate the strong effect of seasonality on paediatric LRTI admissions (245).

The calculation of cloud-modified UVB data by TEMIS has been proven to accurately represent the surface level D-UVB doses in geographical regions (223). By following the process outlined earlier in the methods section of this chapter, TEMIS reliably factors in the major attenuating variables additional to ozone distribution to generate D-UVB data. As a major strength of this study, it could play a significant role in future research investigating the impact of UVB radiation on health. In addition to the annual UVB dose specific to the vitamin D action spectrum, TEMIS provides separate data on UVB wavelengths that cause erythema and DNA damage, as well as seasonal breakdowns for these variables.

As with the analyses in Chapter 5, it was impossible to match the HES and TEMIS data to the same yearly time periods, as HES records admissions starting on April 1st each year while TEMIS calculates annual D-UVB doses starting on January 1st. With no monthly recordings, it was not possible to manipulate the data so that the time periods matched. However, as shown in Figure 6.4 and Figure 6.3, most endogenous synthesis of vitamin D synthesis would not occur during the 3 month period where this mismatching would be a source of error.

The correction for cloud cover brought the association between D-UVB and LRTI admission rates into significance. A limitation of this study is that the effects of other meteorological factors weren't explored in the analyses; hours of sunlight and temperature variables could potentially affect LRTI admission rates and it would be useful to control for these by including them in the model (188). Another factor that could potentially be introduced in future analyses is population exposure to pollution. Different measures of atmosphere pollution shown to affect respiratory health include nitrogen dioxide (NO_2) and varying sizes of particulate matter ($PM_{2.5}$, PM_{10}) (189) (205). Larger molecules such as those included in PM_{10} measurements have also been shown to absorb UVB radiation, further reducing surface exposures which can affect vitamin D synthesis (72).

6.4.2 Implications for clinical practice

The LRTIs that the child population of England were admitted with in this study were acute, and multiple annual LRTIs are common in children (246). The findings of this study could inform risk reduction strategies to avoid multiple severe LRTIs on a population level. Vitamin D supplementation has been shown to be beneficial in protecting against LRTI (191).

Recommendations to parents with regard to helping prevent further LRTI could therefore include supplementation, especially when at a time of year when there is little adequate D-UVB (118). The immunomodulatory effects of vitamin D could enhance anti-viral defence while limiting destructive, pro-inflammatory responses that often exacerbate LRTI (247).

Results from this population scale study adds to evidence to advocate for population scale solutions. Vitamin D deficiency is preventable, as are its detrimental clinical and subclinical effects on child health (105). English populations, partially due to the impact of latitude and seasonality, are vulnerable to these effects in the absence of supplementation especially in vulnerable groups (54) (209). Vitamin D supplementation by recommendation has previously been seen to be ineffective, as few people follow this advice (56). Public health campaigns might see this change, however implementing supplementation as health policy would be far more reliable, and an investment into preventing LRTI on a population level. This also avoids the potential risks of advocating prolonged sunlight exposures in children.

6.5 Summary

In this chapter, analyses carried out have provided a more detailed view of how D-UVB exposures can affect the respiratory health of child populations across England. Increased opportunities available to the population to synthesize vitamin D (higher D-UVB annual doses) were found to be significantly associated with acute LRTI admissions on both GP and CCG levels. The effect found was strong and significant, but only when accounting for meteorological factors that attenuate D-UVB radiation. Socioeconomic deprivation was found to be significant in all analyses, shown to be a potent predictor of poor respiratory health outcomes in children.

7 Discussion

This thesis had the objective of exploring different environmental factors' interactions with common paediatric health conditions. To meet this aim, the thesis became an amalgam of five studies observing relationships using different environmental variables and aggregate admissions data of varying sizes.

Chapters 2, 3 and 4 analysed the associations between changes in large scale regional weather patterns and regional admission rates for three common pathologies seen acutely in children. With some significant associations found between temperature and rainfall variables and both gastroenteritis and lower respiratory tract admission rates, hours of sunshine were found to be significantly associated with all three conditions studied. A major biological determinant of vitamin D status, the duration of population sunlight exposure, was found to influence the risk of asthma, LRTI and gastroenteritis admissions in children. As shown in Table 7.1, the models show that an additional 100 hours of sunshine are associated with a 9.31% reduction in asthma admissions, a 5.87% reduction in LRTI admissions and a 17.5% reduction in gastroenteritis admissions (relative to the mean admission rate for all years).

If the assumption that the effects on admissions of hours of sunshine is completely vitamin D-mediated, ensuring adequate vitamin D status in the English child population could improve health outcomes and significantly reduce costs. For example, it has been estimated that in 2011/12 that £69 million was the cost to the NHS of asthma-related hospital admissions for all ages (248). Asthma UK estimate that children aged 0 to 14 constituted

41.5% of all admissions in 2012 (249). Using these statistics, it can be crudely estimated that paediatric asthma admissions costed £28.7 million in 2011/12, and it can be inferred from our findings that the prevention of vitamin D insufficiency through universal vitamin D supplementation could have saved around £2.67 million. Improving asthma outcomes through measures to improve population vitamin D status could reduce costs incurred in primary care and prescriptions.

The purpose of chapters 5 and 6 was partly to compensate for certain flaws in the regional analysis models investigating environmental effects on asthma and LRTI. These flaws include: not all direct sunlight exposure leads to efficient vitamin D synthesis; large assumptions have to be made when interpreting effects seen in populations of such large geographical blocks; and factors affecting respiratory health such as smoking rates were not controlled for. To address these flaws, several components were required when creating the study. Ultraviolet-B levels specific to the vitamin D action spectrum were used instead of hours of sunshine data; HES admissions data from 7966 GP practices were used instead of PCT or regional data; and maternal smoking rates were included in the multivariate regression models. The study design in these chapters was, therefore, a natural progression from that of the pre-2012 studies.

The results from the analyses in chapters 5 and 6 show a consistently significant negative association between cloud-modified D-UVB and both acute asthma and LRTI admissions in children ($p<0.001$). Comparing the predicted percentage reductions in admission rates upon an annual increase in cloud-modified D-UVB dose by 100kJ/m^2, this change in D-UVB would impact CCG-level asthma admission rates more than it would LRTI, with a 62.9% reduction

relative to the mean rate compared to 30.9% (Table 7.1). By using corrected D-UVB radiation instead of hours of sunshine, the analysis results gave more significant results of greater magnitude, with higher adjusted R^2 values.

While strong associations have been found in this thesis between markers of child health and environmental factors closely linked with the ability of a population to synthesize vitamin D, there are flaws in the research undertaken. Limitations identified by Davies *et al* in their original paper examining acute asthma admissions and hours of sunshine, such as a lack of granularity of data in the 2002/3-2010/11 HES dataset, and controlling for factors such as smoking rates, were addressed in this thesis, however this effort was not completely successful (143). Factors that affect individual vitamin D status, such as obesity, ethnicity and medication use were still not controlled for. Pollution indices are potential variables missing from the analyses, and the HES admissions data were imperfect and impacted the GP-level analyses in particular. Small number suppression and zero inflation likely impacted the results of the chapter 5 and 6 analyses; using CCG aggregate level data appeared to improve the model likely as it mitigated these effects, and appeared to be a better level to accurately view and interpret associations at.

Table 7.1- A table summarising the associations between of different environmental factors and different markers of child health outcomes in this thesis.

	Condition	Variable (+change)	p<0.001	Change in admission rate (per 100,000 per annum)	% change (relative to mean)
2002/3-2010/11	Asthma	HoS (+100)	✓	-27.4	-9.31%
		Rainfall (+100mm)	✗	-	-
		Temperature (+1°C)	✗	-	-
		IDACI (+0.1)	✓	+4.29	+1.62%
	LRTI	HoS (+100)	✓	-22.9	-5.87%
		Rainfall (+100mm)	✓	+11.4	+2.92%
		Temperature (+1°C)	✓	-81.2	-20.8%
		IDACI (+0.1)	✓	-6.34	-1.63%
	Gastroenteritis	HoS (+100)	✓	-241	-17.5%
		Rainfall (+100mm)	✓	-49.4	-3.59%
		Temperature (+1°C)	✓	-185	-13.5%
		IDACI (+0.1)	✗	-	-
2013/14 - 2017/18	Asthma	Cloud-mod UVB (+100kJ/m^2)	✓	-210	-62.9%
		IDACI (+0.1)	✓	+650	+195%
2016/17 - 2018/19	LRTI	Cloud-mod UVB (+100kJ/m^2)	✓	-208	-30.9%
		IDACI (+0.1)	✓	+500	+74.2%

These results have been generated from the regression coefficients given for each analysis. The expected changes in admission rates upon an increase in the variables described are given, with this also expressed as a percentage change compared to the mean admission rate for that condition.

A limitation for each of the ecological studies which constitute this thesis is that of ecological fallacy. Assumptions are made when interpreting the thesis findings which generalise characteristics or risks in the population, limiting how applicable to individuals the results are. The effects of ecological fallacy on the utility of these findings are reduced when using aggregate data of smaller geographical sizes. The analyses at GP and CCG level in chapters 5 and 6, for instance, make far fewer assumptions about the uniformity of the variables used in the statistical model than those in chapters 2, 3 and 4, which use large scale regional data.

Extended generalised estimating equations could not be used as a test for the data used in chapters 5 and 6, as there were too many data observations to include in a panel data analysis. However, as previously discussed, zero-inflated Poisson (ZIP) regression could be used to carry out further analysis of the associations between D-UVB levels and admissions for asthma and LRTI. The results from the analyses of such models would be interesting to interpret, as the impact of zero inflation on the initial linear regression analyses could be retrospectively assessed.

Future research into the influence of environmental factors on child health would benefit from using additional meteorological and pollution covariates alongside TEMIS D-UVB data and paediatric hospital admissions data primarily collected from CCGs to avoid anonymization and excess zero counts. Acute gastroenteritis admissions would be an interesting marker of child health to apply these changes in study design to, as of the three conditions analysed with hours of sunshine, it showed the strongest associations in relative terms. Other chronic immune or acute infective diseases could be researched, investigating the geographical changes seen in admissions (or other markers of health outcomes) and D-

UVB exposures. Indeed, there has been very little investigation into the impact of vitamin D supplementation on gastroenteritis in UK children, and little exploration of the prevalence of vitamin D deficiency in these patients.

Ecological studies such as these are useful to carry out in the UK, as population vitamin D status is highly sensitive to environmental factors. The UK experiences different regional weather patterns (Figure 5.4), with metropolitan centres with high aerosol pollution (205). A relatively temperate climate, mediated by the Gulf Stream, masks the effects of the UK's relatively high latitude on the impaired UVB penetrance through the ozone layer (54). Foods are not fortified with vitamin D, and child supplementation rates in the British population are very low (5-20%) when compared to European countries like Germany (70-90%) or Sweden (90%) (250). With little dietary availability of vitamin D, the vitamin D status of the UK population is highly responsive to environmental changes impacting UVB levels (54). With the recent changes in the proportions of ethnic groups in Europe, unsupplemented populations are more at risk of vitamin D deficiency due to the increased challenge of vitamin D synthesis in individuals with darker skin (55).

Any public health messages on sun exposure from this thesis will have to recognise that there is a risk-benefit assessment that every patient or their family has to make. Too much ultraviolet radiation can be harmful, causing sunburn which can increase the risk of developing skin cancer in later life (251). Advice regarding D-UVB exposure should include consideration of the time of day and year. Long, unprotected exposures to sunlight causing sunburn should be avoided, as vitamin D conversion occurs efficiently during short periods

of exposure (76). Synthesis efficiency peaks well before DNA damage occurs, after all, vitamin D is the evolutionary product of a primordial DNA-protective sunscreen (2) (76).

Research into the effects of vitamin D and its deficiency on asthma and LRTI health outcomes already exists, and the trends identified in this thesis could be used to argue that the effects of vitamin D supplementation should be further researched (118) (127). These results should encourage clinicians, parents and policy-makers to consider vitamin D status as a key health determinant in children, with more effective sun exposure and more universal supplementation being strategies to reduce the health and economic burdens of immune-mediated conditions such as asthma and LRTI.

8 Conclusion

These studies highlight robust statistical evidence that show increased UVB radiation levels are inversely associated with hospital admission rates for several common and important paediatric conditions. The magnitude of these effects is best seen when asthma and LRTI admission rates are analysed with the D-UVB levels, which strengthens the case that these observations are caused by factors which are relevant to vitamin D synthesis. These observations remain significant following adjustment for key confounders.

Hours of sunshine and other regional weather variables are significantly associated with acute gastroenteritis admission rates in children have been found to be significant in real and relative terms. This highlights an avenue for future research into the impact of vitamin D status on gastroenteritis.

Deprivation has been confirmed to be a prominent predictor of poor respiratory health outcomes throughout this thesis. The models created using large datasets have illuminated effects which have previously been difficult to study, making a novel contribution to vitamin D research. The results found in this thesis serve as a reminder of the importance of population health and the potential impact of targeted, evidence based public health measures.

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