

Helmi Ikonen

VITAMIN D STATUS AND
ITS ASSOCIATIONS WITH
DISEASE OVER
THE COURSE OF
ADULTHOOD –
A NORTHERN FINLAND
BIRTH COHORT 1966
STUDY

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UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
MEDICAL RESEARCH CENTER OULU

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HELMI IKONEN

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Academic dissertation to be presented with the assent of the Doctoral Programme Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium K101 of the Faculty of Medicine (Aapistie 7 A), on 29 November 2024, at 12 noon

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Abstract

In Finland, located at high northern latitudes, the amount of vitamin D in the average diet has been increased by systematic vitamin D fortification in common foods such as fluid dairy products and fat spreads since 2006. There is evidence that this had a positive effect on the vitamin D status in the population, but less is known about the determinants associated with the change. The previous knowledge about vitamin D in chronic conditions has also certain limitations, for example, regarding the lack of standardized 25-hydroxyvitamin-D [25(OH)D] measurements. The study populations have been heterogenous, specifically highlighting inpatient and aging populations, especially in studies analyzing psychiatric conditions. Also, there is very limited evidence about the role of vitamin D status in the progression of multimorbidity among the middle-aged population.

The aim of this thesis, conducted with participants of the Northern Finland Birth Cohort 1966 (NFBC1966), was to study the longitudinal change in vitamin D status and related determinants before and after the start of systematic vitamin D food fortification in Finland. Another aim was to study the association of vitamin D with psychiatric conditions in young adulthood and with multimorbidity in middle age.

Among the sample from the 31-year follow-up of the NFBC1966, we found no difference in 25(OH)D concentration between participants with depression, schizophrenia, other psychoses, and controls using standardized vitamin D z-score adjusting for measurement-related covariates.

The second study demonstrated an improvement in vitamin D status following the start of vitamin D food fortification in Finland. This improvement was also observed as a decrease in the seasonal variation in vitamin D status and as the highest increase in 25(OH)D concentrations among those with the lowest 25(OH)D at baseline.

In the third study, we found that, by the age of 54 years, one out of ten of the NFBC1966 population had multimorbidity as measured by the Charlson Comorbidity Index (CCI). Vitamin D status at 46 years predicted multimorbidity at 54 years, but the association was attenuated when adjusting for BMI.

In conclusion, this thesis highlights the improvement in vitamin D status among the Finnish adult population. Still, one individual out of four had 25(OH)D concentrations below 50 nmol/l.

Keywords: food fortification, multimorbidity, observational study, psychiatric conditions, the Northern Finland Birth Cohort, vitamin D

Ikonen, Helmi, Aikuisväestön D-vitamiinitasot ja niiden yhteys sairaustiloihin Pohjois-Suomen syntymäkohortissa 1966

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Tiivistelmä

Suomessa, joka sijaitsee hyvin pohjoisilla leveyspiireillä, ruokavalion D-vitamiinin määrää on lisätty systemaattisesti maitotuotteiden ja rasvaviljojen D-vitamiinirikastuksella vuodesta 2006. Aiempien löydösten perusteella tällä on ollut myönteinen vaikutus väestön D-vitamiinitasoihin, mutta muutokseen liittyvistä tekijöistä on vähemmän tietoa. Aiemmissä tutkimuksissa D-vitamiinitasojen yhteydestä pitkäaikaissairauksiin on myös puutteita, kuten vakioitujen 25-hydroksivitamiini-D [25(OH)D] -mittausten puuttuminen. Tutkimusaineistot ovat olleet vaihtelevia korostaen sairaalapotilaista ja iäkkäistä koostuneita aineistoja, erityisesti psykiatrisia sairaustiloja koskevissa tutkimuksissa. Myös D-vitamiinitasoista suhteesta monisairastavuuteen keski-ikäisessä väestössä on vähän aiempaa tietoa.

Tässä Pohjois-Suomen syntymäkohortissa 1966 suoritetussa väitöstutkimuksessa tavoitteeni oli tutkia D-vitamiinitasojen muutoksia ajan kuluessa ja D-vitamiinitasoihin liittyviä tekijöitä ennen ja jälkeen systemaattisen D-vitamiinirikastuksen aloitusta. Muissa tutkimuksen osatöissä tavoitteena oli tutkia D-vitamiinitasojen yhteyttä psykiatrisiin sairaustiloihin nuorena aikuisuudessa sekä monisairastavuuteen keski-ikässä.

Ensimmäisessä osatyössä hyödynsimme otosta kohortin seurantatutkimuksesta 31 vuoden iässä. Siinä ei havaittu merkittäviä eroja masennusta, skitsofreniaa tai muita psykooseja sairastavilla verrattuna vertailuväestöön. Löydös säilyi ennallaan käyttäen vakioitua D-vitamiini z-arvoa, joka oli muodostettu hyödyntäen mittaukseen liittyviä kovariaatteja.

Toinen osatyö havainnollisti D-vitamiinitasojen nousua systemaattisen D-vitamiinirikastuksen myötä. Myönteinen muutos oli havaittavissa myös D-vitamiinitasojen vuodenaikavaihtelun vähenemisenä ja suurimpana D-vitamiinitason parannuksena niiden joukossa, joiden seerumin 25(OH)D pitoisuudet olivat lähtötilanteessa matalimpia.

Kolmannen osatyön löydösten mukaan yhdellä kymmenestä kohortin osallistujasta todettiin monisairastavuutta Charlsonin komorbiditeetti-indeksin perusteella. D-vitamiinitasot 46 vuoden iässä ennustivat monisairastavuutta 54 vuoden iässä, mutta tämä yhteys hävisi, kun tulos korjattiin painoindeksillä.

Johtopäätöksenä tämä väitöstutkimus korostaa D-vitamiinitasojen kohentumista suomalaisessa aikuisväestössä. Siitä huolimatta yhdellä neljästä todettiin 25(OH)D pitoisuus alle 50 nmol/l.

Asiasanat: D-vitamiini, havainnoiva tutkimus, monisairastavuus, Pohjois-Suomen syntymäkohortti, psykiatriset sairaudet

To Ella, Amanda, and Hilla

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30.10.2024

Helmi Ikonen

List of abbreviations

1,25(OH) ₂ D	1,25-dihydroxyvitamin-D
25(OH)D	25-hydroxyvitamin-D
BMI	body mass index
CCI	Charlson Comorbidity Index
CI	confidence interval
CMIA	chemiluminescence microparticle immunoassay
CV	coefficient of variation
CYP	the cytochrome P450 family
D ₂	ergocalciferol
D ₃	cholecalciferol
DBP	vitamin D binding protein
FGF23	fibroblast growth factor 23
HR	hazard ratio
ICD	international classification of diseases
IL	interleukin
IOM	the Institute of Medicine
IQR	interquartile ratio
IU	international unit
LC-MS/MS	liquid chromatography tandem mass spectrometry
MET	metabolic equivalent task
NFBC	the Northern Finland Birth Cohort
NNC	the Nordic Nutrition Council
OR	odds ratio
PCOS	polycystic ovary syndrome
PTH	parathyroid hormone
RCT	randomized controlled trial
RDA	recommended daily allowance
RIA	radioimmunoassay
SD	standard deviation
SEP	socioeconomic position
UV	ultraviolet
VDR	vitamin D receptor
VDSP	vitamin D standardization programme
WC	waist circumference

List of original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

- I Ikonen, H.*, Palaniswamy, S.*, Nordström, T., Järvelin, M. R., Herzig, K. H., Jääskeläinen, E., Seppälä, J., Miettunen, J., & Sebert, S. (2019). Vitamin D status and correlates of low vitamin D in schizophrenia, other psychoses and non-psychotic depression - The Northern Finland Birth Cohort 1966 study. *Psychiatry Research*, 279, 186–194. <https://doi.org/10.1016/j.psychres.2019.02.060>
- II Ikonen, H.*, Lumme, J.*, Seppälä, J., Pesonen, P., Pilttonen, T., Järvelin, M. R., Herzig, K. H., Miettunen, J., Niinimäki, M., Palaniswamy, S., Sebert, S., & Ojaniemi, M. (2021). The determinants and longitudinal changes in vitamin D status in middle-age: a Northern Finland Birth Cohort 1966 study. *European Journal of Nutrition*, 60(8), 4541–4553. <https://doi.org/10.1007/s00394-021-02606-z>
- III Ikonen, H., Rautio, N., Miettunen, J., Sebert, S., & Seppälä, J. (2024). Vitamin D status and multimorbidity; a Northern Finland Birth Cohort 1966 study. Manuscript.

*These authors contributed equally.

Publication II is included in the doctoral thesis of Johanna Lumme.

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1 Introduction

Vitamin D is a fat-soluble molecule that is well known for its action in maintaining calcium balance and bone mineralization (Wacker & Holick, 2013). Solar UV-B radiation is needed for the cutaneous synthesis of vitamin D and is the main source of vitamin D in humans (Holick, 2007). Variations in serum 25(OH)D concentrations, currently the most used indicators of vitamin D status, have been demonstrated worldwide. Such variations might result from latitudinal and seasonal differences between studies, differences in food fortification policies, supplementation use, cultural and dietary habits, age range, and ethnicity (van Schoor & Lips, 2017; Wahl et al., 2012).

In the northern latitudes, where the daylight is reduced over a long winter period, the dietary intake of vitamin D-rich foods and oral supplementation are essential sources of this fat-soluble prohormone to prevent vitamin D deficiency (Huotari & Herzig, 2008; Wacker & Holick, 2013). Unfortunately, few natural food products (fish, egg yolk, and certain wild mushrooms) contain significant amounts of vitamin D. To ensure an adequate vitamin D status in their populations, the Nordic countries (i.e., Finland, Sweden, Norway, Denmark, and Iceland) have launched vitamin D food fortification programs by systematically adding vitamin D to non-organic dairy products, fat spreads, breakfast cereals, and certain baby foods (Itkonen et al., 2018; Itkonen et al., 2021). There is evidence that systematic Finnish vitamin D food fortification has improved the vitamin D status of the population (Jääskeläinen et al., 2017), but there is less knowledge about factors associated with longitudinal change in vitamin D status and, especially, about the determinants of vitamin D deficiency in a generally vitamin D-replete population.

In addition to the well-known role of vitamin D in bone metabolism, publications during the last two decades have produced accumulating evidence of its association with several chronic conditions, including type 2 diabetes (Lips, 2001), cardiovascular diseases (Jani et al., 2021; Zhang et al., 2017), autoimmune diseases (Antico et al., 2012), and certain cancers (Mondul et al., 2017). Vitamin D status has also been associated with both depression and schizophrenia in several studies. Systematic reviews and meta-analyses about the association of serum 25(OH)D concentration and the risk of depression and schizophrenia have reported an increased odds ratio of both depression and schizophrenia for deficient versus sufficient vitamin D status (Anglin et al., 2013; Valipour et al., 2014). However, there is a large amount of heterogeneity in the studies included in the systematic reviews and meta-analyses. Moreover, the studies concerning vitamin D status and

depression include mainly older adults, and studies about vitamin D status and schizophrenia consider more in- than outpatients.

It has been suggested that vitamin D status might act as a biomarker of overall ill health (Autier et al., 2014; Caristia et al., 2019). Indeed, higher 25(OH)D concentrations have been associated with several positive health and behavior characteristics: normal weight, healthy diet, physical activity, and time spent outdoors (Hintzpeter et al., 2008; Jääskeläinen et al., 2013). Against this background, it seems relevant that vitamin D deficiency has been suggested to be associated with multimorbidity, which is usually defined as the existence of two or more co-occurring conditions. To date, the relationship between vitamin D status and multimorbidity has not been studied in detail. Findings from a Dutch population-based cohort suggested an association between low serum 25(OH)D concentrations and a higher prevalence of multimorbidity (Meems et al., 2015). Two retrospective studies among geriatric hospitalized populations have been conducted and shown conflicting results (Boccardi et al., 2019; Moo et al., 2020). Based on these earlier findings, there is a lack of research among the non-geriatric general population utilizing comprehensive data on morbidity status.

In this interesting and developing research environment, this doctoral thesis has developed and investigated the role of vitamin D status in an aging adult population at the start of a systematic program of vitamin D food fortification.

2 Literature review

Vitamin D has been studied extensively in the last few decades, although the discovery of this fat-soluble, hormone-like vitamin occurred a century ago. The recent studies on vitamin D have been extensive, focusing on mechanisms and definitions, associations of vitamin D status with different conditions and disease characteristics, and the therapeutic potential of vitamin D supplementation.

2.1 A brief history of vitamin D

In the early 1900s, several scientists came to the idea that food consisted of another element in addition to macronutrients. The “vital amins,” later called vitamins, were discovered (Funk, 1912).

The discovery of vitamin D was closely related to the study of rickets. Rickets, a bone-deforming disease especially affecting children, had already been observed in the 17th century (Bouillon & Antonio, 2020; Polyandri a Kerchoven J, 1684) Findings about the effect of cod liver oil and ultraviolet radiation in the treatment of rickets helped lead the way to the discovery of vitamin D. This work was completed by McCollum in 1922, when he studied heated cod liver oil, which lost its vitamin A activity but still had the capability of healing rickets (McCollum et al., 1922).

2.1.1 History of vitamin D fortification

Soon after the discovery of vitamin D, scientists Hess and Steenbock conducted experiments regarding the UV irradiation of food items (Hess & Weinstock, 1924; Steenbock & Black, 1924). Both this method and the addition of vitamin D₂, ergosterol, to foods represented the start of vitamin D food fortification in the 1920s. Milk was the most important product already fortified by the 1930s, along with a range of other products also enriched with vitamin D. However, at the beginning of the 1950s, reports of hypercalcemia and mild intellectual disability in infants led to wide bans on vitamin D fortification internationally (Holick, 2023; “Infantile Hypercalcaemia, Nutritional Rickets, and Infantile Scurvy in Great Britain,” 1964). Later, it was discussed and proposed that, in addition to an increased intake of vitamin D, the etiology of the syndrome was related to intrinsic hypersensitivity to vitamin D (Holick, 2023; Schlingmann et al., 2011).

In the last few decades, fortification has been restarted primarily in countries located at northern latitudes. Currently, Finland, Sweden, Norway, Canada, the United States, and a few other countries undertake food fortification with vitamin D. Today's practice of vitamin D fortification and existing related policies are discussed more thoroughly in section 2.3.3.

2.2 Vitamin D status

2.2.1 Definition of vitamin D status

According to current consensus, serum 25(OH)D concentration is used as a biomarker of individual- and population-level vitamin D status. Other biomarkers have been studied, but, to date, serum 25(OH)D is considered the most robust measure when estimating vitamin D status. One central justification for this is that 25(OH)D responds in a dose-responsive manner to endogenous and supplemental vitamin D in its different forms (Seamans & Cashman, 2009). The sum of 25(OH)D₂ and 25(OH)D₃ constitutes the total 25(OH)D concentration. The concentration of 25(OH)D can be expressed in nmol/l or ng/ml as follows:

- 1 nmol/l = 0.4 ng/ml
- 1 ng/ml = 2.5 nmol/l.

Vitamin D status is considered sufficient when serum 25(OH)D levels > 50 nmol/l or > 20 ng/ml (Ross et al., 2011). The terminology used to describe vitamin D status at serum 25(OH)D levels < 50 nmol/l varies. Some reviews conclude concentrations < 50 nmol/l represent vitamin D deficiency (Amrein et al., 2020; Bouillon, 2017; Holick et al., 2011; Lips et al., 2019), while others consider this situation vitamin D insufficiency or inadequacy (Munns et al., 2016). 25(OH)D concentrations < 25–30 nmol/l or < 12 ng/ml are considered severely deficient (Amrein et al., 2020; Munns et al., 2016). Vitamin D deficiency should be avoided to prevent the development of nutritional rickets in children and osteomalacia in adults. Vitamin D toxicity, leading to hypercalcemia and related organ disturbances, can be detected when serum 25(OH)D levels exceed 250–375 nmol/l (Amrein et al., 2020; Munns et al., 2016).

There has been debate about the health benefits of higher serum 25(OH)D concentrations. The current cut-offs for vitamin D status categories have been defined by examining the relationship of 25(OH)D concentrations with calcium

absorption, bone turnover markers, and parathyroid hormone (PTH) excretion, which is inversely associated with serum 25(OH)D levels. Also, the definitions are based on insights from studies on the associations of serum 25(OH)D and health outcomes (Lips et al., 2019; Munns et al., 2016; Ross et al., 2011). Regarding bone health, 25(OH)D concentration 40 nmol/l is sufficient for 50% and 50 nmol/l for 97.5% of the general population (Ross et al., 2011). According to the Endocrine Society, 25(OH)D concentrations of 50–75 nmol/l have been classified as insufficient and > 75 nmol/l as sufficient vitamin D status (Holick et al., 2011). However, this recommendation has been formulated from a clinical point of view and regarding the pleiotropic effects of vitamin D. Currently, there seems to be no clear evidence for using this cut-off in population-level studies (Lips et al., 2019). The serum 25(OH)D cut-offs used in different definitions of vitamin D status are shown in table 1.

Table 1. Definitions of vitamin D status according to different institutions.

Definition	Institute of Medicine (Ross et al., 2011)	Endocrine Society (Holick et al., 2011)	The European Calcified Tissue Society (Lips et al., 2019)	Global Consensus Statement on Prevention and Management of Nutritional Rickets (Munns et al., 2016)
Severe deficiency			< 30 nmol/l	
Deficiency	< 30 nmol/l	< 50 nmol/l	< 50 nmol/l	< 30 nmol/l
Insufficiency		50–75 nmol/l		30–50 nmol/l
Sufficiency	≥ 50 nmol/l	≥ 75 nmol/l	≥ 50 nmol/l	≥ 50 nmol/l

In this thesis, I refer to vitamin D sufficiency as serum 25(OH)D levels ≥ 50 nmol/l, vitamin D deficiency as serum 25(OH)D levels < 50 nmol/l, and severe vitamin D deficiency as serum 25(OH)D levels < 30 nmol/l.

2.2.2 Vitamin D status worldwide

Vitamin D deficiency has been discussed as a pandemic over the last decade (Cashman et al., 2016; Holick, 2017). This discussion has been related to the debate regarding the definition of vitamin D status as well as increasing knowledge about the risk groups for low 25(OH)D concentrations. In previous publications estimating worldwide vitamin D status, the estimates range widely across studies. The general trend shows vitamin D deficiency as less common in North America,

Australia, and Northern and Western Europe and more prevalent in Southern Europe, Africa, the Middle East, and Asia (Hilger et al., 2014; Lips et al., 2019; Oskarsson et al., 2022; Wahl et al., 2012). The estimates vary among different samples and laboratory techniques, but the prevalence of vitamin D deficiency (< 50 nmol/l) in adults varies between 24–40% in North America, Australia, and Northern and Western Europe. Severe deficiency (< 30 nmol/l) is found in 6–13% of these areas. In Southern Europe, Africa, the Middle East, and Asia, the prevalence of vitamin D deficiency in adults is reported to vary from 30 to 90% and that of severe deficiency from 6 to 36% (Hilger et al., 2014; Lips et al., 2019; Manios et al., 2018; Mogire et al., 2020). Systematic reviews conclude on a paucity of studies concerning vitamin D status among children and adolescents, especially in developing countries and among general population samples (Palacios & Gonzalez, 2014; Wahl et al., 2012). However, the current state of knowledge suggests that children, pregnant and lactating women, institutionalized older adults, and non-Western immigrants are risk groups for vitamin D deficiency (Hilger et al., 2014; Lips et al., 2019; van Schoor & Lips, 2017; Wahl et al., 2012).

2.2.3 Determinants of vitamin D status

Different factors affect individual and population 25(OH)D concentrations via either vitamin D synthesis, intake, or metabolism. Factors influencing the amount of UV-B radiation reaching the skin also play a major role. Additionally, geographical location and the season of the year are strongly associated with vitamin D status (Khanna et al., 2022; Macdonald, 2013; WEBB et al., 1988). Latitude affects the angle at which solar UV-B radiation reaches the Earth, which in turn affects the distance that the radiation must travel to reach the Earth's surface (Wacker & Holick, 2013). At northern latitudes, the maintenance of adequate vitamin D status is impossible without dietary or supplement sources. Northwards from the latitude of 50 °, which corresponds with northern France and the southernmost parts of Canada, vitamin D synthesis in the skin is practically undetectable during the winter period from October to March (WEBB et al., 1988).

Other factors affecting the amount of UV-B reaching the skin include the amount of clothing one wears and the amount of time spent outdoors, skin pigmentation, and the use of sunscreen. Melanin causes skin pigmentation and results in the absorption of UV radiation. This is speculated to lead to lower vitamin D synthesis. In accordance with this hypothesis, lower serum 25(OH)D levels have been found among dark-skinned populations, especially among non-Western

immigrants (Ames et al., 2021; Mendes et al., 2019; Munns et al., 2016; van Schoor & Lips, 2017). However, it is not well-identified whether the higher prevalence of vitamin D deficiency among dark-skinned populations is due to a lower rate of vitamin D synthesis or, alternatively, genetic or cultural factors (Scientific Advisory Committee on Nutrition, 2016).

Also, age affects skin properties, which is potentially resulting in poorer dermal vitamin D synthesis in older age. Other factors leading to lower 25(OH)D concentrations among older persons include impaired liver and kidney function as well as decreased time spent outdoors and other behavioral factors (Brouwer-Brolsma et al., 2016; Scientific Advisory Committee on Nutrition, 2016; van Schoor & Lips, 2017).

Sunscreen blocks the ability of UV-B radiation to infiltrate the skin, which results in a lower rate of dermal vitamin D synthesis. However, there have also been reports of higher 25(OH)D concentrations among sunscreen users versus non-users (Brouwer-Brolsma et al., 2016; Hyppönen & Power, 2007). This finding could likely reflect the fact that people using sunscreen spend plenty of time in the sun. It might also be related to other behavioral patterns like greater health awareness among sunscreen users, which could affect vitamin D status positively. Moreover, it has been concluded that even though sunscreen use can theoretically reduce the production of vitamin D in an individual, this is mostly not considered a significant problem (Norval & Wulf, 2009).

Today, an important confounder of vitamin D status is obesity. A high BMI has been consistently associated with vitamin D deficiency (Pereira-Santos et al., 2015; Rafiq & Jeppesen, 2018; Saneei et al., 2013) and inversely associated with the response to vitamin D supplementation (de Oliveira et al., 2020). The inverse association of BMI and serum 25(OH)D concentrations has been explained by differences in metabolism and behavior in overweight and obese individuals. The expression of hepatic 25-hydroxylase enzyme CYP2R1 seems to be depressed in obesity, decreasing the activation step of circulating 25(OH)D (Roizen et al., 2019). It has also been suggested that vitamin D metabolites could be sequestered in fat tissue before hydroxylation steps crucial for vitamin activation (Cheng et al., 2010).

There is no clear evidence of a sex-related difference in vitamin D status. Nevertheless, in some parts of the world, there is a tendency for women to have lower serum 25(OH)D concentrations compared to males (Hilger et al., 2014). This could be related to cultural habits for women to use covering clothing or to spend time mainly indoors. However, pregnant and lactating women seem to be at a higher risk of vitamin D deficiency (Lips et al., 2019; van Schoor & Lips, 2017).

2.3 Vitamin D intake

2.3.1 Recommendations for vitamin D intake

The current recommendations for vitamin D intake vary across countries based on local circumstances (*e.g.*, geographical location, diet, culture, and other habits). Examples of these recommendations are presented in table 2. The 2010 the Institute of Medicine (IOM) report published the recommended daily allowance (RDA) of vitamin D, which should cover the daily need for at least 97.5% of the US population. The RDAs for vitamin D were 400 international units (IU) (corresponding to 10 µg daily) for infants under 1 year, 600 IU (15 µg/day) for age groups from 1 year to 70 years, and 800 IU (20 µg/day) for adults 70 years and older (Ross et al., 2011). This IOM report has been discussed (Cashman & Kiely, 2014; Holick et al., 2011), but most current guidelines follow the IOM recommendations with respect to the current knowledge.

Table 2. Vitamin D recommendations for reference intake and supplementation in different countries.

Country	Reference intake	Supplementation
Finland (Finnish Food Authority, 2020)	10 µg/d for 1–75 years, 20 µg/d for > 75 years, specific recommendation for infants	10 µg/d, 7.5 µg/d for 2–17 years, 20 µg/d for > 75 years
Sweden (Livsmedelsverket., 2023)	10 µg/d for 0–75 years, 20 µg/d for > 75 years and for specified risk groups	10–20 µg/d for specified risk groups with low vitamin D intake or inadequate sunlight exposure
Iceland (Directorate of Health Iceland., 2023)	10 µg/d for children from 1–2 weeks of age to 9 years, 15 µg/d from 10 to 70 years, 20 µg/d > 70 years	Supplementation is recommended especially in winter but also in summer if sun protection is used
The United Kingdom (The National Health Service The United Kingdom., 2020)	8.5 µg/d for babies up to 1 year of age, 10 µg/d for children > 1 year and adults	10 µg/d from October to April upon individual consideration and for risk groups with inadequate sunlight exposure
The United States (National Institutes of Health - Office of Dietary Supplements, 2024)	10 µg/d for infants to 12 months, 15 µg/d from 1 to 70 years, 20 µg/d > 70 years	

2.3.2 Natural sources of vitamin D

Sunlight represents a major source of vitamin D in humans. It is estimated that sunlight in the summer season accounts for 70–90% of total vitamin D intake (Holick, 2007). Vitamin D intake is further affected by several factors discussed above in chapter 2.2.3.

There are a few natural dietary sources of vitamin D. Fatty fish, egg yolk, and some wild mushrooms contain amounts that are considered significant (Finnish Institute of Health and Welfare & Finnish Food Composition Database). However, the intake from these sources is generally too low to meet the need of vitamin D except for some cultural practices (fish-consuming cultures, *e.g.*, Inuit). Vitamin D is present as D₂ (ergocalciferol) in plants and as D₃ (cholecalciferol) in animal-derived sources. Table 3 shows a comparison of vitamin D content in different dietary vitamin D sources.

Table 3. Vitamin D in different dietary sources (Finnish Institute of Health and Welfare & Finnish Food Composition Database).

Source	Amount of vitamin D per 100 g
Funnel chantarelle, fried	19.0 µg
Perch, fried	16.8 µg
Vendace, fried	9.9 µg
Egg	2.2 µg
Vegetable hash, potato, and mushroom	1.9 µg
Butter, no fortification	0.3 µg
Milk, no fortification	< 0.1 µg

2.3.3 Vitamin D fortification

Countries located at northern latitudes have implemented vitamin D food fortification programs—either mandatory or voluntary. Fortified products are usually dairy products and their plant-based alternatives, fat spreads, cereals, and orange juice. The current fortification policies in the Nordic countries are presented in table 4. In addition to the Nordic countries, at least Canada and the US in North America and some countries in the Middle East region (Jordan, Kuwait, Saudi Arabia, United Arab Emirates) use some degree of food fortification with vitamin D (Cashman, 2021).

Table 4. Vitamin D food fortification policies in the Nordic countries.

Product	Finland	Sweden	Norway	Denmark	Iceland
	(Itkonen et al., 2018; Itkonen et al., 2021)	(Itkonen et al., 2021; Summerhays et al., 2020)	(Nasjonalt råd for ernæring, 2006)	(Grønberg et al., 2019, 2020)	(Itkonen et al., 2021)
Fluid milk products	2002: 0.5 µg/100 g 2010: 1 µg/100 g fluid milk products, lactose-free and vegetable-based alternatives, yoghurt, sourmilk	2007: Extra low-fat milk (< 1.5% fat) 0.38–0.5 µg/100 g 2018: milk, fermented milk (≤ 3% fat), including lactose-free and vegetable-based alternatives 0.75–1.1 µg/100 g	2006: Extra low-fat and lactose-free milk, 0.4 µg/100 g	No systematic fortification	No systematic fortification
Fat spreads	2002: 10 µg/100 g 2010: 20 µg/100 g	2007: margarine and cooking fats 7.5–10 µg/100 g 2018: 19.5–21.0 µg/100 g	2006: 10 µg/100 g	No systematic fortification	No systematic fortification
Other				Fortification allowed since 2005 in fat spreads, sports drinks, and lactose-free milk products.	Some milk products, some domestic foods (most fat spreads), and some imported foods (vegetable oils, cereals) are fortified.

As stated earlier, systematic vitamin D fortification in Finland started in 2002. The National Nutrition Council (NNC) of Finland granted approval for (i) all fluid dairy products (excluding organic) and respective plant-based alternatives to be systematically fortified with 0.5 µg/100 ml and (ii) all fat spreads, excluding butter, to be systematically fortified with 10 µg/100 g vitamin D₃ (Lamberg-Allardt et al., 2006). This policy was evaluated in 2006 by comparing serum 25(OH)D concentrations in Finnish population in 2002 and 2004 as well as before fortification and one year after the start of fortification. Despite the increase in the intake of vitamin D after the first fortification wave, 21.3% of the studied population still had serum 25(OH)D levels below 50 nmol/l. Among the study participants who reported no vitamin D supplementation, the proportion was one third (Lamberg-Allardt et al., 2006). After this evaluation, the amount of added vitamin D was doubled in the second fortification wave in 2010 (1.0 µg/100 ml of D₃ in fluid dairy products and plant-based alternatives, 20 µg/100 g of D₃ in fat spreads). In line with the earlier evaluation, Finnish investigators found the second fortification wave to have a further positive effect on vitamin D status in the population (Jääskeläinen et al., 2017). However, the studies in Sweden and Norway, which also use some degree of vitamin D food fortification, did not find significant change in vitamin D status over time (Jorde et al., 2010; Summerhays et al., 2020). The fortification policies have not been as systematic as in Finland, which might in part explain the difference.

2.3.4 Vitamin D supplementation

Vitamin D supplementation can be in the form of either ergocalciferol D₂ or cholecalciferol D₃. In the existing RCTs, vitamin D supplementation is administered as D₂ or D₃ in various doses and frequencies from 400 IU daily to 500 000 IU as a single dose. In some trials, vitamin D has also been combined with calcium and/or omega-3. D₂ and D₃ have been compared in terms of their efficacy in increasing serum 25(OH)D concentrations, and, according to the current knowledge, D₃ is more efficacious across population groups studied and various methods of administration (Balachandar et al., 2021; Tripkovic et al., 2012).

The current recommendations for vitamin D supplementation vary between countries. Some countries have general vitamin D supplementation recommendations, while others include different recommendations for population subgroups. Some countries have no distinct recommendations for supplementation apart from the general reference intake for vitamin D. In Finland, the general

recommendation is 10 µg/d during the winter for those not already consuming a vitamin D-rich diet. There is also a recommendation of daily supplementation throughout the year for infants and children and for elderly adults ≥ 70 years old (Finnish Food Authority, 2020). Table 2 provides more examples of the existing recommendations.

2.4 Vitamin D metabolism

2.4.1 Synthesis and absorption, transportation

In humans, vitamin D is synthesized in the skin from 7-dehydrocholesterol as a response to UV-B radiation or is obtained from dietary or supplementary sources. In general, dermal synthesis is the most important source. The reaction starts when UV-B radiation catalyzes the conversion of 7-dehydrocholesterol to cholecalciferol, also known as D_3 . D_3 flows in the circulation and, upon arriving at the liver, is further hydroxylated by 25-hydroxylase to $25(OH)D_3$. Dietary or supplemental vitamin D is digested in the form of either plant-derived D_2 or animal-derived D_3 . Once absorbed in the small intestines, it is transported to the liver in chylomicrons and hydroxylated to $25(OH)D_2$ and $25(OH)D_3$. These two forms differ structurally in their side chains but seem to behave in a similar manner in the body and are usually summed as total $25(OH)D$ when discussing vitamin D status (Ross et al., 2011).

The chain of hydroxylations continues when $25(OH)D_2$ and $25(OH)D_3$ arrive in the kidney and are metabolized to $1,25(OH)_2D_2$ or $1,25(OH)_2D_3$, respectively. This reaction is catalyzed by the enzyme 27B1 of the cytochrome P450 family (CYP27B1) (Bikle & Christakos, 2020). From this point on, I will use the term total $1,25(OH)_2D$ to reflect the sum of $1,25(OH)_2D_2$ or $1,25(OH)_2D_3$. Several different vitamin D metabolites have been distinguished (Jenkinson et al., 2021), but, so far, the most important biologically active metabolite of vitamin D is $1,25(OH)_2D$.

The enzyme CYP24A1 is responsible for the degradation of $1,25(OH)_2D$. After 24-hydroxylation, it turns into calcitric acid. CYP24A1 also has the ability to inactivate $25(OH)$ into biologically inactive $24,25(OH)_2D$ (Schlingmann et al., 2011). Figure 1 is summarizing the main pathways of vitamin D synthesis and absorption.

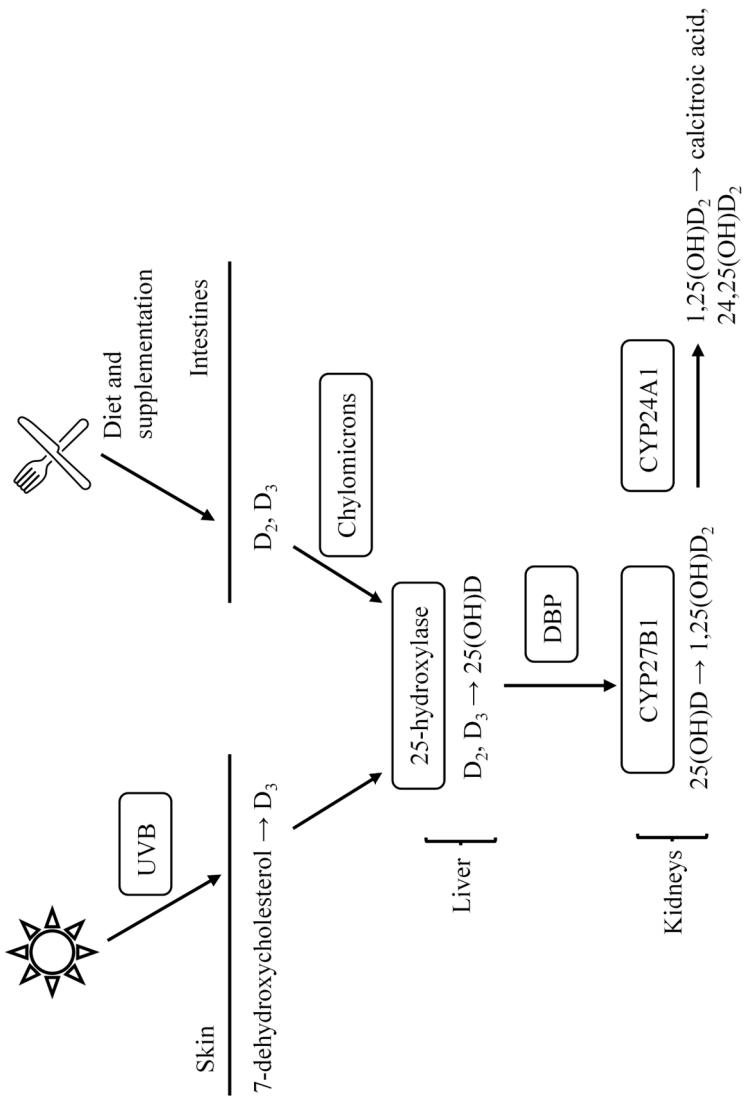


Fig. 1. The main pathways of vitamin D synthesis and absorption.

In the circulation, 25(OH)D is largely bound to vitamin D binding protein (DBP), constituting 85% of the total circulating 25(OH)D. Fifteen percent is bound to albumin and only 0.03% exists as free 25(OH)D (Bikle & Schwartz, 2019). According to the free-hormone hypothesis, it is only the free, non-bound fraction that can cross the cell membranes freely (Bikle & Schwartz, 2019). In some tissues, mainly in the kidneys, the DBP-bound 25(OH)D is transported to the cells by megalin-cubulin complex (Nykjaer et al., 1999).

2.4.2 Regulation and mechanisms of vitamin D action

1,25(OH)₂D synthesis occurs in the kidneys but also in various other tissues throughout the body in both a paracrine and autocrine manner. In the kidneys, CYP27B1, the enzyme responsible for 1,25(OH)₂D formation, is suppressed by 1,25(OH)₂D itself, calcium, phosphate, and bone-derived fibroblast growth factor 23 (FGF23). Again, PTH is an inducer of CYP27B1. Reciprocally, 1,25(OH)₂D and FGF23 induce CYP24A1, which catalyzes the degradation of 1,25(OH)₂D while PTH suppresses it (Meyer & Pike, 2020). In extrarenal tissues, the regulation of 1,25(OH)₂D production seems to differ from these principles (Bikle, 2014). It has been suggested that the actions of 1,25(OH)₂D can be divided into hormone and cytokine functions from an evolutionary perspective (Adams & Hewison, 2012). The hormone functions are linked to the renal production of 1,25(OH)₂D and the cytokine functions to extrarenal production in, for example, macrophages, which are under the control of immune factors.

Vitamin D exerts its action via vitamin D receptor (VDR), which is widely expressed in human tissues. VDR is a nuclear receptor and usually forms a heterodimer with retinoid X receptor when bound by its ligand, 1,25(OH)₂D (Bikle, 2014). This heterodimer binds to the vitamin D-responsive elements of DNA and activates the transcription of various genes (Meyer et al., 2010).

The main action of vitamin D is to maintain stable serum calcium concentrations. Low 1,25(OH)₂D stimulates calcium and phosphorus absorption in the intestines, reabsorption of calcium in the renal distal tubules, and mobilizes calcium from the skeleton. Dietary calcium is used first to balance the serum calcium, but if this does not fill the need, endogenous sources are then used (DeLuca, 2004).

PTH, secreted from parathyroid gland, is tightly related to vitamin D metabolism. The classic action of PTH is to maintain serum calcium concentrations and bone remodeling acting on bone and distal tubule in the kidney (Evenepoel et

al., 2016). As stated above, PTH is regulating the enzymes responsible for vitamin D metabolism. Low 25(OH)D concentrations can cause increased PTH concentrations, called secondary hyperparathyroidism, which in turn cause high bone turnover, bone loss, mineralization defects, and hip and other fractures (Lips, 2001).

2.5 Associations between vitamin D status and disease

Beyond its skeletal activity, vitamin D has been suggested to play a role in several extraskeletal processes. VDR has been detected in nearly all tissues with nucleated cells, and the activation of VDR is related to the transcription of multiple genes (Bouillon et al., 2019). Several pathways, including anti-inflammatory, antiproliferative, and antioxidative actions, have been identified to support the role of vitamin D in different pathological processes (Bouillon et al., 2019). For example, the antioxidative effect has been consistent in immune cell studies showing suppression of key inflammatory markers, such as macrophage chemotactic protein 1, interleukin (IL)-6, and IL-8 (Calton et al., 2015). Preclinical studies have shown antiproliferative actions along with other mechanisms of tumor suppression, including inhibition of angiogenesis, induction of apoptosis, and a decrease in inflammation and metastasis (Bouillon et al., 2019). Regarding cardiovascular disease, vitamin D has been found to decrease vascular inflammation, endothelial dysfunction, and smooth muscle proliferation (Cosentino et al., 2021). Vitamin D is also a suppressor of the renin-angiotensin-aldosterone system and an inhibitor of secondary hyperparathyroidism, which could lead to an antihypertensive effect (Mozos & Marginean, 2015).

In line with these observations from preclinical data, observational studies have shown lower vitamin D status to be associated with autoimmune diseases (Antico et al., 2012) and cancers (Mondul et al., 2017) as well as total cardiovascular disease (Jani et al., 2021; Zhang et al., 2017), type 2 diabetes (Lips et al., 2017; Mohammadi et al., 2022), and all-cause mortality (Liu et al., 2022).

To date, vitamin D supplementation has not been shown to be effective in the treatment of these conditions based on RCT primary analysis findings apart from some evidence for a reduction in mortality (Cao et al., 2023; Liu et al., 2022; Santos et al., 2023). In secondary analyses of the D2D trial, vitamin D supplementation decreased the risk for type 2 diabetes in trial participants who maintained serum 25(OH)D concentrations ≥ 100 nmol/l compared to those with lower levels of 50–74 nmol/l (Dawson-Hughes et al., 2020). It has been debated that, in many cases,

the design of RCTs has been biased due to overlooking pretrial vitamin D status and BMI, incomplete information about total vitamin D intake, and not considering achieved 25(OH)D concentration in the estimation of treatment effect (Grant et al., 2022). It has also been suggested that, due to the discrepancy in the results of observational studies and RCTs, serum 25(OH)D would act as a biomarker of ill health (Autier et al., 2014).

In Mendelian randomization studies, vitamin D status has not been causally associated with most studied chronic conditions, including cancers (Lawler & Warren Andersen, 2023), type 1 and type 2 diabetes (Manousaki et al., 2021; Wang, Wang et al., 2020), cardiovascular and mortality outcomes (Emerging Risk Factors Collaboration/EPIC-CVD/Vitamin D Studies Collaboration, 2024), but genetically low 25(OH)D concentrations have been shown to increase the risk for multiple sclerosis (Mokry et al., 2015). The results from a recent review of linear Mendelian randomization studies strongly support the causal association between vitamin D and multiple sclerosis, while the role in other chronic conditions remains suggestive (Fang et al., 2024). Also recently, non-linear Mendelian randomization studies have been conducted in the UK Biobank data, in which a causal association was suggested between vitamin D and cardiovascular disease, dementia, and mortality in serum 25(OH)D concentrations < 50 nmol/l (Navale et al., 2022; Sutherland et al., 2022; Zhou et al., 2022). However, the methods used in these studies have been under debate (Burgess, 2023; Smith, 2023).

No association was found with genetic low 25(OH)D variants and asthma, cardiovascular mortality, colorectal and breast cancer, and all-cancer incidence in an umbrella-review of observational studies, RCTs, and Mendelian randomization studies. However, vitamin D supplementation decreased the risk for all-cause mortality (Liu et al., 2022). An earlier umbrella review including observational studies and RCTs concluded that, while the evidence is inconclusive regarding several health outcomes, associations between 25(OH)D concentrations and birth weight, dental caries in children, maternal 25(OH)D concentrations at term, and PTH concentrations in patients with chronic kidney disease requiring dialysis are probable (Theodoratou et al., 2014).

Based on current knowledge, vitamin D deficiency observed in those with several chronic conditions seems to be more a consequence than a cause of the disease. Nevertheless, it is important to detect and correct vitamin D deficiency to prevent possible long-term consequences related to inadequate vitamin D status.

2.5.1 Vitamin D in psychiatric conditions

Mood disorders, especially depression, are an important public health concern among working-aged adults. Psychotic disorders are less frequent but cause substantial individual and societal burden. The global age-standardized prevalence of depression was 3 440 per 100 000 people and that of schizophrenia 287 per 100 000 people (GBD 2019 Mental Disorders Collaborators, 2022). In Finland, the prevalence of depression has not been estimated very recently, but, in Health 2011 data, 7.4% of adults had a depressive disorder (Markkula et al., 2015). The lifetime prevalence of schizophrenia and all psychotic disorders in Finland was 0.87% and 3.5%, respectively (Perälä et al., 2007).

Mechanistic studies have shown increasing interest in the role of vitamin D in psychiatric disorders. VDR has been found to be widely expressed in the human brain, where it is the most abundant in the hypothalamus and substantia nigra (Eyles et al., 2005). Vitamin D has also been found to have neuroprotective effects, for example by inhibiting the synthesis of tumor necrosis factor- α and IL-6 (Lefebvre d’Hellencourt et al., 2003). *In vitro* studies have indicated that vitamin D could regulate neurotransmission via tyrosine metabolism and thereby affect dopaminergic signaling (Kesby et al., 2017). These findings link vitamin D to depression and schizophrenia pathogenesis, which have been associated with dopaminergic dysregulation. Animal models have also given clues that vitamin D could prevent the development of dysregulated dopaminergic phenotypes in vulnerable individuals (Luan et al., 2018).

In support of these findings, observational studies have found an association between 25(OH)D concentrations and depression (Anglin et al., 2013), schizophrenia (Valipour et al., 2014; Zhu et al., 2020), and other neuropsychiatric disorders, such as autism spectrum disorder (Wang et al., 2016; Wang, Ding et al., 2020) and Alzheimer’s disease (Shen & Ji, 2015). A meta-analysis of observational studies on vitamin D and depression was published 10 years ago (Anglin et al., 2013). It found a 1.31-fold (95% CI 1.00, 1.71) increased OR of non-psychotic depression in individuals in the lowest *versus* the highest vitamin D category. Among the three cohort studies included, they found a hazard ratio (HR) of 2.21 (95% CI 1.40–3.49) for depression in the lowest *vs.* the highest vitamin D category. The majority of studies were conducted among older adults.

Several systematic reviews and meta-analyses about the effect of vitamin D supplementation on depression have been conducted (Gowda et al., 2015; Guzek et al., 2023; Li et al., 2014; Mikola et al., 2022; Shaffer et al., 2014; Spedding, 2014;

Xie et al., 2022). Possibly due to the heterogeneity of interventions, differences in the severity of depression, baseline vitamin D status of the samples, and use of vitamin D supplementation along with durations, and dosages, the findings seem contradictory; however, it seems that vitamin D supplementation could reduce depressive symptoms.

A higher risk for developing schizophrenia in males who did not receive vitamin D supplementation during infancy was detected in the Northern Finland Birth Cohort 1966 (NFBC1966) (McGrath et al., 2004). However, the role of vitamin D in the pathogenesis of schizophrenia can be different in infancy and adulthood (McGrath et al., 2010). Valipour et al. meta-analyzed the existing knowledge about vitamin D in schizophrenia from observational studies. They reported a significant difference in serum 25(OH)D concentrations between their schizophrenia and control group groups. However, this finding was observed only among inpatients, not outpatients, and most of the study subjects were inpatients (Valipour et al., 2014). A more recent meta-analysis repeated the finding of a difference in vitamin D status between the schizophrenia patients and controls. Their meta-regression analysis pointed out that BMI could explain some degree of heterogeneity between studies (Zhu et al., 2020). A Mendelian randomization study based on summary data from genome-wide association studies of 34 241 schizophrenia cases and 45 604 controls did not support a causal association of vitamin D deficiency and schizophrenia, while the risk for schizophrenia per 10% increase in serum 25(OH)D was 0.99 (95% CI 0.96, 1.02) (Taylor et al., 2016). In line with this finding, the meta-analyzed results of RCTs did not find vitamin D effective in the treatment of schizophrenia in two trials (Xu et al., 2022).

The association between vitamin D and other psychoses was summarized in 2014 by Belvederi-Murri et al. No difference was found in vitamin D status between other psychoses and controls. Comparing vitamin D status in schizophrenia and other psychoses, a trend towards lower serum 25(OH)D concentrations in schizophrenia was observed, but this finding was not significant (Belvederi Murri et al., 2013).

In conclusion, there is a large amount of heterogeneity in the studies included in the systematic reviews and meta-analyses investigating the associations between vitamin D status and non-psychotic depression, schizophrenia, and psychotic disorders. Also, most studies have been conducted in older depression patients and, regarding schizophrenia, among inpatients rather than outpatients.

2.5.2 Vitamin D in multimorbidity

Multimorbidity is most often defined as the coexistence of two or more chronic conditions, but the methods to define multimorbidity in the research context vary greatly (Ho et al., 2021; Johnston et al., 2019). A systematic review identified 33 unique multimorbidity instruments used in 96 different studies assessing the association of multimorbidity with different outcomes used (Lee et al., 2021). Among the instruments, Disease Count and different weighted indices, such as Charlson comorbidity index (CCI), were most used (Lee et al., 2021). Another systematic review and meta-analysis included 566 studies and summarized multimorbidity definitions used in these studies (Ho et al., 2021). 36.4% of included studies did not report a reference definition for multimorbidity and 12.9% of the studies did not report the conditions included in the multimorbidity definition. Two out of three studies were using simple disease counts, while the rest of the studies utilized weighted indices, combinations of simple counts and weighted indices or the method remained unclear (Ho et al., 2021).

Due to the heterogenous nature of multimorbidity definition, the estimates of overall prevalence vary. Recent studies have concluded the prevalence to be from 37 to 42% (Chowdhury et al., 2023; Ho et al., 2022). However, by age, the prevalence was significantly lower, 28%, in the age group < 59 years (Ho et al., 2022), and by region, the highest prevalence was found in South America followed by North America, Europe and Asia (Chowdhury et al., 2023).

The progression of multimorbidity has been suggested to be associated with systemic inflammation. In a national sample of middle-aged and older adults from the United States, multimorbidity was positively associated with inflammation markers and functional limitations, and inflammation partially mediated the association between multimorbidity and functional limitations (Friedman et al., 2015). An Italian longitudinal study among participants aged 60 years and older found that higher baseline IL-6 levels and steeper increases in IL-6 levels were significantly associated with a steeper increase in multimorbidity during follow-up (Fabbri et al., 2015). As described above, vitamin D has been found to be involved in different inflammatory processes, such as the suppression of IL-6 (Calton et al., 2015).

Another factor associated with both vitamin D and multimorbidity is obesity. A systematic review and meta-analysis of observational studies about vitamin D status in obesity found a 35% higher prevalence of vitamin D deficiency in subjects with obesity (Pereira-Santos et al., 2015). In a Finnish study, replicated in UK

Biobank data, the degree of obesity was associated with complex multimorbidity (four or more comorbid conditions) in a dose-response manner (Kivimäki et al., 2022). However, the relationship between vitamin D status and multimorbidity has not been studied in detail to date.

A Dutch population-based cohort, the Lifelines cohort, studied the association between serum 25(OH)D concentrations and multimorbidity. Multimorbidity was defined by a self-developed composite morbidity score. They found that lower serum 25(OH)D concentrations were associated with a higher morbidity score that included 12 disease categories (Meems et al., 2015). A retrospective, cross-sectional study among a geriatric hospitalized population found an inverse correlation between serum 25(OH)D levels and the Cumulative Illness Rating Scale-Comorbidity Index, meaning a higher comorbidity burden associated with lower vitamin D status. 25(OH)D concentrations were measured in the participants at admission to a geriatric acute care unit (Boccardi et al., 2019). Another retrospective, cross-sectional study conducted in a geriatric hip-fracture population found no relationship between CCI score and vitamin D levels (Moo et al., 2020). Thus, there is a lack of studies about vitamin D and multimorbidity in a non-selected, general population sample utilizing comprehensive diagnosis information and multimorbidity measures which allows for comparison with existing knowledge.

2.6 Vitamin D studies in the NFBC

Vitamin D studies using NFBC data published in the last two decades are listed in table 5. At the moment, all vitamin D studies in NFBC have been conducted using the NFBC1966 data. The earlier studies used the questionnaire information about vitamin D supplementation in infancy, whereas the later studies (*i.e.*, from 2016 onward) used serum 25(OH)D concentrations from the clinical examinations at the 31-year and 46-year follow-ups.

Table 5. Publications related to vitamin D in NFBC.

Study title	Year of publication	Conclusion
Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study (Hyppönen et al., 2001)	2001	Dietary vitamin D supplementation in the first year of life was associated with reduced risk of type 1 diabetes.
Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study (McGrath et al., 2004)	2004	Vitamin D supplementation during the first year of life was associated with a reduced risk of schizophrenia in males.
Infant vitamin D supplementation and allergic conditions in adulthood: Northern Finland Birth Cohort 1966 (Hyppönen et al., 2004)	2004	The study observed an association between vitamin D supplementation in infancy and an increased risk of atopy and allergic rhinitis later in life.
Does vitamin D supplementation in infancy reduce the risk of pre-eclampsia? (Hyppönen et al., 2007)	2007	The risk of pre-eclampsia was halved in participants who had received vitamin D supplementation regularly during the first year of life.
High-dose vitamin D supplements are not associated with linear growth in a large Finnish cohort (Hyppönen et al., 2011)	2011	Neither the frequency nor dose of vitamin D supplementation was associated with height at 14 or 31 y.
25-hydroxyvitamin D concentration and leukocyte telomere length in young adults: findings from the Northern Finland Birth Cohort 1966 (Williams et al., 2016)	2016	25(OH)D levels were not associated with leukocyte telomere length in either basic or adjusted models.
Serum 25-hydroxyvitamin D status and longitudinal changes in weight and waist circumference: influence of genetic predisposition to adiposity (Larsen et al., 2016)	2016	Analysis of the NFBC1966 showed that 25(OH)D levels at baseline were inversely associated with changes in body weight.
Harmonization study between LC-MS/MS and Diasorin RIA for measurement of 25-hydroxyvitamin D concentrations in a large population survey (Berry et al., 2017)	2017	Concentrations measured by LC-MS/MS were much higher than those measured by Diasorin RIA.
Potential determinants of vitamin D in Finnish adults: a cross-sectional study from the Northern Finland Birth Cohort (Palaniswamy et al., 2017)	2017	Risk factors for low vitamin D status were low sunlight exposure defined by time of sampling, residing at northern latitudes, obesity, higher waist circumference, low physical activity, and unhealthy diet.

Study title	Year of publication	Conclusion
Dairy- and supplement-based calcium intake in adulthood and vertebral dimensions in midlife - the Northern Finland Birth Cohort 1966 Study (Oura et al., 2019)	2019	Longitudinal vitamin D intake estimated from dietary and supplemental sources from age 31 to 46 years was ascending among the majority of the sample.
Vitamin D status and correlates of low vitamin D in schizophrenia, other psychoses and non-psychotic depression - The Northern Finland Birth Cohort 1966 study (Ikonen et al., 2019)	2019	The study did not find a difference in vitamin D status between schizophrenia, psychoses, non-psychotic depression, and control groups.
Vitamin D levels in women with polycystic ovary syndrome: a population-based study (Lumme et al., 2019)	2019	PCOS was associated with higher vitamin D levels when adjusting for confounding factors, without distinct beneficial effects on metabolic derangements.
Could vitamin D reduce obesity-associated inflammation? Observational and Mendelian randomization study (Palaniswamy et al., 2020)	2020	The findings did not support a beneficial role of vitamin D supplementation in obesity-related inflammation.
The determinants and longitudinal changes in vitamin D status in middle-age: a Northern Finland Birth Cohort 1966 study (Ikonen et al., 2021)	2021	An increase of 10.6 nmol/l in serum 25(OH)D was observed, the prevalence of vitamin D insufficiency was halved, and the seasonal deviation was reduced.
Non-occupational exposure to pesticides and health markers in general population in Northern Finland: Differences between sexes (Palaniswamy et al., 2021)	2021	No association was found between pesticide exposure and vitamin D.
Vitamin D status in women with a history of infertility and decreased fecundability: a population-based study (Lumme et al., 2023)	2023	Previous infertility and decreased fecundability were associated with lower 25(OH)D levels.
Vitamin D and multimorbidity: a Northern Finland Birth Cohort 1966 study (Ikonen et al., manuscript)	2024	Middle-aged patients with multimorbidity have a higher risk for vitamin D deficiency, even though the association seems to be confounded by BMI.

3 Aims of the present study

The aim of this doctoral study was to investigate vitamin D status during adulthood and in chronic conditions. The study is characterized by a unique research environment with comprehensive data from the NFBC1966 follow-up studies preceding and following the start of systematic food fortification with vitamin D in Finland.

Study I

Considering the inconsistency as well as great heterogeneity in previous studies on the subject, we aimed to investigate vitamin D status in depression, schizophrenia, and other psychoses in a general population sample.

Study II

As there is a paucity of studies addressing the possible independent effect of food fortification on vitamin D status in the general population, we aimed to explore the determinants of and longitudinal change in the vitamin D status of a population under fortification. One aim in this study was also to address risk factors associated with vitamin D deficiency among generally vitamin D replete population.

Study III

There is lack of studies concerning the association of vitamin D status and multimorbidity, which represents an important public health burden. Thus, the intention of this study was to explore whether vitamin D status is associated with the accumulation of diseases among a middle-aged general population with sufficient mean 25(OH)D concentrations.

4 Materials and methods

4.1 Study population

The data used in this doctoral work is from the NFBC1966, which represents genetically most isolated regions in Finland (Sabatti et al., 2009). The study invited all pregnant women with expected delivery dates in 1966 living in Northern Finland (provinces of Oulu and Lapland). A total of 12 231 children (95.6% of all births in the area, according to Statistics Finland) were recruited. Of this number, 173 were stillborn, resulting in a final total of 12 058 live-born children included in the follow-up. The follow-up studies were conducted when the participants were at the age of 1, 14, 31, and 46 years. Postal questionnaires including questions about lifestyle, socioeconomic position, and somatic and mental health were sent to the participants. They were also invited to clinical examinations, including routine measurements (*e.g.*, height, weight, blood pressure), blood sampling, and other measurements (*e.g.*, lung function tests). More detailed information along with an overall description of the NFBC1966 is available elsewhere (Nordström et al., 2022). The utilized data is derived from the 31- and 46-year follow-up studies, as presented in table 6.

Table 6. Data sources for the NFBC1966 used in the thesis.

Follow-up study	Study I	Study II	Study III
31 years			
Postal questionnaire	X		
Clinical examination	X	X	
Register data	X		
46 years			
Postal questionnaire		X	X
Clinical examination		X	X
Register data (up until 2020)			X

The study population in study I included participants who had undergone clinical examination in the 31-year follow-up study, had available 25(OH)D₂ and 25(OH)D₃ measurements at 31 years, and had available information regarding the covariates used in the analysis. The final sample included 4 987 participants categorized into depression ($n = 264$), schizophrenia ($n = 40$), other psychoses ($n = 24$), and control ($n = 4 659$) groups.

Study II included NFBC1966 participants who had available 25(OH)D measurements at both ages of 31 and 46. A total of 3 650 participants were included in the final analyses.

Study III analyzed a sample comprising those who had attended the 46-year follow-up study, had 25(OH)D concentrations available, and had given their written consent to use their existing register data along with the cohort data. The number of participants included was 5 540. A flow chart from the study population is shown in figure 2.

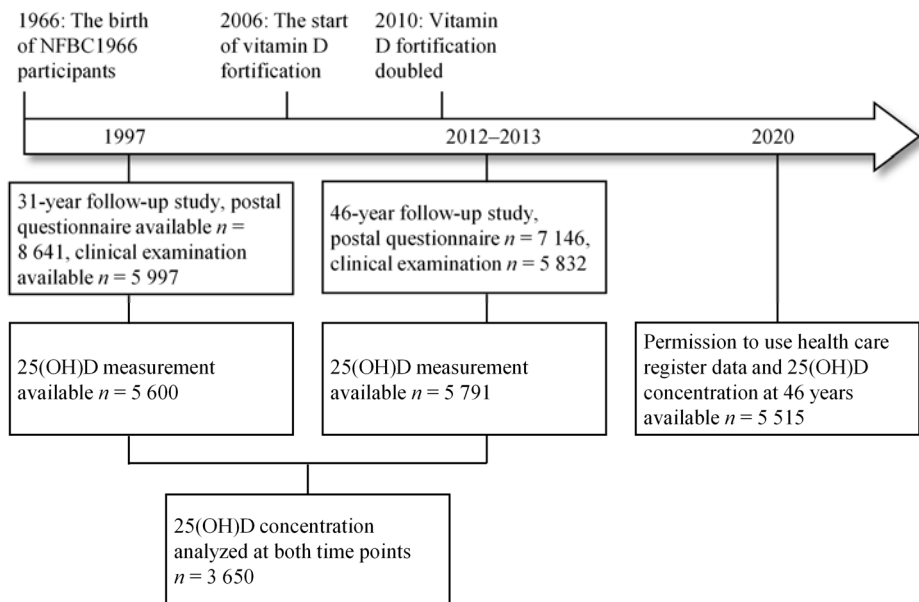


Fig. 2. Flow chart of the study population.

4.2 Vitamin D assessment

Blood samples, preceded by an overnight fast, were drawn between 8 am and 11 am during the clinical examination visits of the 31- and 46-year follow-up studies. The samples were frozen at -70°C until analysis. To determine the serum 25(OH)D concentrations at 31 years, the blood samples were analyzed in four batches using liquid chromatography tandem mass spectrometry (LC-MS/MS; Elstree, Hertfordshire, UK). The concentrations of 25(OH)D₂ and 25(OH)D₃ were analyzed

separately, with their sum constituting the total 25(OH)D concentration. These measurements were used in study I.

A subset of 31-year blood samples was later analyzed with a chemiluminescence microparticle immunoassay (CMIA) Architect i2000SR automatic analyzer (Abbott Diagnostics), which has been certified according to the Center for Disease Control and Prevention's Vitamin D Standardization-Certification Program (VDSP) (Sempos et al., 2012). An equation was calculated to convert all the 31-year 25(OH)D concentrations to VDSP-calibrated concentrations (Durazo-Arvizu et al., 2017), which were then used in the final analyses of study II.

At the 46-year follow-up, serum 25(OH)D concentrations were analyzed using Architect i2000SR automatic analyzer (Abbott Diagnostics), and these measurements were used in studies II and III. The coefficient of variation (CV) from the repeated quality-control samples was calculated, and the resulting CV for internal control samples was $\leq 3.6\%$ across the working range.

The cut-offs used for vitamin D status in the studies differed based on the aim of the study and deviations in the serum 25(OH)D concentration in the population at the time of the study. In study I, vitamin D status was categorized according to the IOM criteria: < 30 nmol/l (deficient), $30\text{--}50$ nmol/l (insufficient), and ≥ 50 nmol/l (sufficient) (Ross et al., 2011). Vitamin D status was also assessed by the quartiles of serum 25(OH)D concentration. In study II, vitamin D status was categorized in four categories, < 30 nmol/l, $30\text{--}50$ nmol/l, $50\text{--}75$ nmol/l, and ≥ 75 nmol/l. In study III, we categorized vitamin D status into two groups: deficient when serum 25(OH)D < 50 nmol/l and sufficient when ≥ 50 nmol/l.

4.2.1 Vitamin D z-score

To control for the effect of measurement-related covariates on serum 25(OH)D, we standardized the serum 25(OH)D concentrations as z-scores adjusting for sex, seasonal, geographical, and technical variation (batch correction for 31-year measurements). The z-scores were calculated separately in the different combinations of these variables' categories. The resulting z-scores were combined into one variable, and these z-score variables of 31-year measurements were used in study I and those of the 31- and 46-year measurements in the regression analysis of study II.

4.3 Disease information

4.3.1 Psychiatric conditions

The diagnoses for study I were collected using the Care Register for Health Care (inpatient treatments until 2013), Finnish outpatient registers (specialized care 1998–2013, primary care 2011–2013), the Finnish Center for Pensions (disability pensions until 2013), and the Social Insurance Institution registers (reimbursable medicines until 2005, disability pensions until 2000, and sick days until 1999). The diagnosis codes used are from the International Statistical Classification of Diseases and Related Health Problems (ICD): ICD–8 (until 1986), ICD–9 (1987–1995), and ICD–10 (since 1996). Table 7 summarizes the diagnosis codes used to determine each condition. Substance-induced and organic psychoses were excluded from other psychoses group based on their different etiology.

Table 7. Definitions of psychiatric conditions by ICD codes used.

Definition	ICD-8	ICD-9	ICD-10
Schizophrenia	2950–2959, 297	2950–2959, 297	F20, F22, F24, F25
Other psychoses	2960–2969, 2980–2983, 2988, 2989, 299	2962E–2964E, 2967, 2961E, 2988, 2989	F23, F28, F29, F302, F312, F315, F323, F333
Non-psychotic depression	2960, 2980, 3004, 7902	2961, 3004	F32 (except F323), F33 (except F333), F341, F3810

4.3.2 Multimorbidity

To define a multimorbidity measure for study III, we chose a validated tool, CCI, which is a weighted index originally developed to predict 10-year breast cancer mortality (Charlson et al., 1987). We used the adaptation for ICD-10 data with respective ICD-9 diagnoses (Sundararajan et al., 2004) and classified the index into three categories of 0, 1, or ≥ 2 . Table 8 shows the diseases, their respective ICD-9 and ICD-10 codes, and the weights for each disease in the CCI.

For disease information, register diagnoses were collected using the Care Register for Health Care (inpatient treatments until 2020) and Finnish outpatient registers (specialized care 1998–2020, primary care 2011–2020). Disease information goes up to 2020, when the NFBC1966 study population is at the age of 54.

Table 8. ICD-9 and ICD-10 diagnoses in the CCI and weights used in the index.

Disease	ICD-9	ICD-10	Weight
Acute myocardial infarction	410, 412	I21, I22, I252	1
Congestive heart disease	428	I50	1
Peripheral vascular disease	441, 4439, 7854, V434	I71, I790, I739, R02, Z958, Z959	1
Cerebral vascular accident	430–438	I60–I66, G450–G452, G454, G458, G459, G46, I670–I672, I674–I679, I681, I682, I688, I69	1
Dementia	290	F00–F02, F051	1
Pulmonary disease	490–496, 500–505	J40–J47, J60–J66	1
Connective tissue disorder	7100, 7101, 7104, 7140–7142, 71481/5171, 725, 725	M32, M332, M34, M050–M053, M058–M060, M063, M069, M353	1
Peptic ulcer	531–534	K25–K28	1
Liver disease	5712, 5714–5716	K702, K703,	
Diabetes	2500–2503, 2507	E109, E119, E139, E149, E101, E111, E131, E141, E105, E115, E135, E145	1
Diabetes complications	2504–2506	E102, E112, E132, E142 E103, E113, E133, E143 E104, E114, E134, E144	2
Paraplegia	342, 3441	G81 G041, G820, G821, G822	2
Renal disease	582, 5830–5837, 585, 586, 588	N03, N052–N056, N072–N074, N01, N18, N19, N25	2
Cancer	14–16, 18, 170–172, 174–176, 179, 190–194, 1950–1955, 1958, 200–208	C0–C3, C40, C41, C43, C45–C49, C5, C6, C70–C76, C80–C85, C883, C887, C889, C900, C901, C91–C93, C940–C943, C9451, C947, C95, C96	2
Metastatic cancer	196–198, 1990, 1991	C77–C90	3
Severe liver disease	5722–5724, 5728	K721, K729, K766, K767	3
Hiv	042–044	B20–B24	6

4.4 Covariates

The covariates for the studies were chosen based on previous literature (Jääskeläinen et al., 2013; Palaniswamy et al., 2017) and a hypothesis about relevant confounders in the studied associations with vitamin D. The covariates used in the studies can be categorized as follows:

1. Vitamin D measurement-related covariates: season of blood sampling, latitude of residency, technical variation (batch correction in 31-year measurements)
2. Background factors: sex, socioeconomic position (SEP), educational status
3. Lifestyle factors: smoking, alcohol consumption, physical activity, diet
4. Anthropometry: body mass index (BMI), waist circumference (WC)
5. Vitamin D intake: vitamin D intake from diet, vitamin D supplementation
6. Medication data: oral contraceptive use, antipsychotic and antidepressive medication use
7. Study-specific covariates: psychiatric treatment days, onset age of psychiatric condition

Season of blood sampling was defined based on the date of the participants' clinical examination, when the blood sampling was conducted. The seasons were categorized as the winter season (November–May) and summer season (June–October) (Seasons in Finland).

The participants' latitude residence was based on the time of the follow-up study in 2012–2013. Residency was derived from the Finnish population register center and was categorized as 60°N (Helsinki and other provinces of middle and southern Finland), 65°N (the city of Oulu), and $\geq 65^\circ\text{N}$ (other northernmost provinces of Oulu and Lapland) (Palaniswamy et al., 2017).

25(OH)D laboratory analysis at 31 years was conducted in four batches. The batch information was used as a technical covariate in the calculation of vitamin D score.

SEP was categorized based on participants' reported current occupational status from the postal questionnaires. This data was categorized as higher-level employees, lower-level employees/entrepreneurs, manual workers/farmers, and non-workers (if pensioner, student, long-term unemployed, or not defined). Educational status was collected from the postal questionnaires and categorized into three groups: basic, secondary, and higher level.

Information concerning participant smoking status, alcohol consumption, and physical activity was also collected from the postal questionnaires. Smoking status was categorized as regular smokers, previous smokers, and non-smokers. Alcohol consumption was expressed as the consumption (g/day) of beer, wine, and spirits in the six months prior to completing the questionnaire (Vladimirov et al., 2016). Alcohol intake was further categorized as low-risk and high-risk categories using the cut-off of 20 g/day for females and 40 g/week for males (World Health Organization. Alcohol, 2022). Physical activity was calculated based on the

frequency and duration of leisure time activities as a metabolic equivalent of task (MET) scores in hours per week (Suija et al., 2013). In study III, physical activity was defined as active with 2.5 hours or more of brisk exercise per week and low if less than that (UKK Institute, The Finnish Physical Activity Recommendation, 2024).

The participants' height (cm), weight (kg), and waist circumference (cm) were measured by trained nurses during the clinical examination. BMI (kg/m^2) was calculated as weight (kg) divided by the square of height (meters). If this clinical examination information was missing, the postal questionnaire was used for height and weight information. The self-reported and clinically measured BMI values were verified and found to provide similar results (Ollila et al., 2016).

Medication information was collected from the postal questionnaire according to participant responses about their present medications and dosages as prescribed by their doctor. Method of contraception in female participants was categorized as no contraception, oral contraceptive pills, and other kind of contraception (Morin-Papunen et al., 2008). The information about psychiatric medication was categorized as no antipsychotic or antidepressive medication, antipsychotic medication, and antidepressive medication. Postal questionnaire data versus pharmacy data regarding psychoactive medication has been estimated previously in this cohort and was considered methodical to use in the studies (Haapea et al., 2010).

4.4.1 Vitamin D intake

Participants' dietary intake of vitamin D at the age of 46 was evaluated based on the postal questionnaire questions regarding food consumption over the previous six months. The National Food Composition Database in Finland, maintained by the National Institute for Health and Welfare (Finnish Institute of Health and Welfare & Finnish Food Composition Database), was used to evaluate the natural vitamin D content of dairy products, spreadable fats, and fish, the principal sources of vitamin D in a typical Finnish diet. The following questions from the questionnaire were used to estimate this information:

How many glasses (0.2 L) do you usually drink/eat per day of: 1. Milk, 2. Sour milk, 3. Other dairy products (e.g., yoghurt, other fermented milk products, ice cream)?

What type of bread spread do you usually use? How many times do you eat bread per day? How much spread do you put on a slice of bread?

How often do you normally consume the following foodstuffs? Oily fish (e.g., salmon, rainbow trout, herring, eel, anchovy, mackerel), medium-fat fish (e.g., whitefish, bream, vendace, flatfish, Baltic herring, common roach, tuna), low-fat fish (e.g., pike, pike perch, perch, burbot, cod, coalfish)

The amount of vitamin D in dairy products except cheese was estimated to be 1 µg per 100 g. In fat spreads, the vitamin D content differs depending on the type of spread: butter and organic butter contain 0 µg/g, vegetable oil spreads and plant-based sterol and stanol margarines 0.2 µg/g, and vegetable oil mixtures 0.1 µg/g.

The vitamin D content of fish was estimated based on information for the 10 most consumed fish and their vitamin D content from the Finnish National Food Composition Database (Finnish Institute of Health and Welfare & Finnish Food Composition Database). The frequency of fish consumption among study participants was assessed via the questionnaire, and the amount of vitamin D was approximated to be 13.4 µg/d if fish was consumed almost daily, 3.8 µg/d if twice a week, and 1.9 µg/d if once a week. Less than once a week was estimated to be 0 µg.

Eggs can also be considered a source of vitamin D in the diet. However, I did not calculate egg consumption in terms of total vitamin D intake, since in this study population, 78% of participants reported eating eggs once a week or less (once a week corresponding 0.3 microg/d).

The use of vitamin D supplementation at 46 years was assessed via the postal questionnaires. The question about the use of vitamins, nutritional supplements, and medications was open-ended. Actual vitamin D supplements, multivitamins, calcium, and omega-3 supplements were considered as vitamin D supplementation, and their vitamin D content was assessed.

The following information was used in the estimation of vitamin D supplementation: the name of the product, the amount of vitamin D in the product reported by the participant, or if missing, by the product manufacturer. The frequency of supplementation was classified as “regular use” if the participant reported vitamin D supplementation use daily or regularly. All other answers regarding frequency (e.g., “every other day”, “twice a week”, “during dark time”) were considered “irregular.” Answers indicating the frequency of vitamin D supplementation, but not the product name or vitamin D amount, were included ($n = 76$).

In the analysis, we used the information about vitamin D supplementation categorized as “non-user,” “irregular,” and “regular” and dietary vitamin D intake as continuous variables ($\mu\text{g}/\text{d}$).

4.5 Statistical analysis

Across the studies, we compared the descriptive characteristics in the study groups using Pearson’s chi-square for categorical variables. For continuous, normally distributed variables, we used an independent samples t-test for two-group comparisons and one-way analysis of variance for multiple-group comparisons. For continuous variables with a skewed distribution, we used a nonparametric Mann–Whitney U test for two-group comparisons and the Kruskal–Wallis test for more than two groups. The distributions of the variables were assessed visually using histograms and statistically using the Kolmogorov–Smirnov test. Statistical significance was set at $p < 0.05$ (two-sided).

4.5.1 Study I

In study I, we analyzed the serum 25(OH)D concentrations categorized into quintiles using the quintile cuts for the 20th, 40th, 60th, and 80th percentiles. The differences in quintiles between the controls versus schizophrenia and other psychoses groups were compared using Fischer’s exact test due to the small size of the schizophrenia and other psychoses groups. Between the control group and non-psychotic depression group, we used a Chi-square test for comparing the serum 25(OH)D quintiles. The vitamin D z-score was used to study the correlations with anthropometric (BMI, WC) and lifestyle variables (smoking, physical activity, alcohol, diet), SEP and psychiatric treatment days. Pearson’s correlation coefficients were used for normally distributed variables and Spearman’s rho for categorical variables. The statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

4.5.2 Study II

In this study, we used a multivariable linear regression analysis with the 46-year vitamin D z-score as the dependent variable and the intakes of fluid dairy products, fat spreads, and fish, vitamin D supplementation use, BMI, and 31-year vitamin D z-score as independent variables. As a sensitivity analysis, a similar regression

analysis including the outlier data was run in addition to one excluding females using oral contraceptives and hormonal replacement therapy due to evidence of a difference in 25(OH)D levels among this group (Lumme et al., 2019; Palaniswamy et al., 2017). The statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25 (IBM Corp. Armonk, NY)

4.5.3 Study III

We studied the association of vitamin D status and multimorbidity using an ordinal logistic regression, where multimorbidity, measured as CCI until the study population reached the age of 54, was set as a dependent variable. Vitamin D status, classified using the cut-off of 50 nmol/l, was set as an independent variable. Vitamin D status 25(OH)D \geq 50 nmol/l was the reference category. ORs and 95% CIs for multimorbidity (CCI \geq 2) were calculated. The association was estimated in three different models.

- Model 1 included vitamin D status, season of blood sampling, latitude of residency, and sex as independent variables.
- Model 2 included model 1 and SEP, alcohol consumption, smoking status, physical activity, and vitamin D supplementation.
- Model 3 included model 2 and BMI.

An additional analysis was also carried out based on a hypothesis that BMI would act as a modifier in the relationship between vitamin D status and multimorbidity. For this, model 2 was stratified by BMI using a cutoff of 30 kg/m². The analyses were run using IBM SPSS Statistics for Windows, Version 29 (IBM Corp. Armonk, NY).

5 Results

The study settings and main results of the sub-studies are summarized in figure 3.

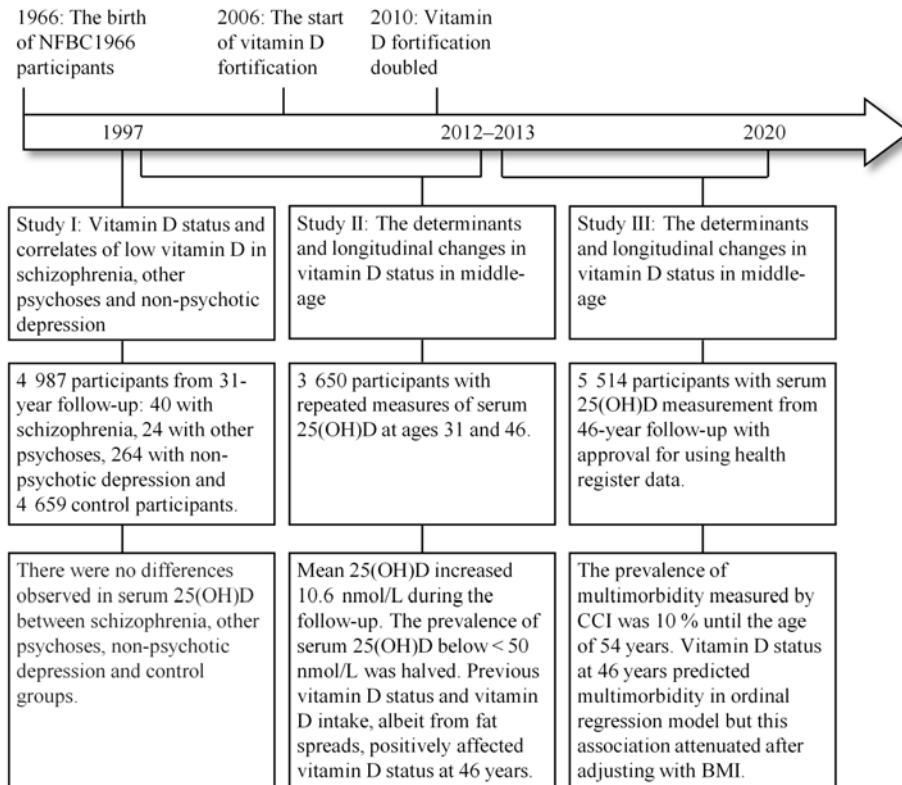


Fig. 3. The study settings and main results of the sub-studies.

5.1 Vitamin D status and correlates of low vitamin D in schizophrenia, other psychoses, and non-psychotic depression (Study I)

5.1.1 Descriptive characteristics of the study population

The study population comprised 4 987 subjects, of which 40 participants had schizophrenia, 24 other psychotic disorders, and 264 non-psychotic depression.

The control population consisted of 4 659 participants. In terms of significant differences in descriptive characteristics, the group with schizophrenia had the highest proportion of participants living in rural areas (75%) compared to the other study groups. The highest proportion of capital region inhabitants (23%) was found in the non-psychotic depression group. The SEP in the group with schizophrenia differed significantly from the other groups in having fewer professional and skilled workers (5%). BMI was higher in the schizophrenia group and in the non-psychotic depression group compared to the control group (26.2 vs. 25.2 kg/m² vs. 24.6 kg/m², respectively). Physical activity was lower in the schizophrenia group compared to the other groups. In terms of other lifestyle factors, the groups did not differ. Schizophrenia and other psychoses groups had the highest number of psychiatric treatment days (median of 93 and 30 days, respectively) and the highest frequency of antipsychotic users (41% and 27%, respectively).

5.1.2 Vitamin D status in the study population

In the study population, the prevalence of severe vitamin D deficiency (serum 25(OH)D < 30 nmol/l) was 3%, the prevalence of vitamin D insufficiency (25(OH)D 30–50 nmol/l) was 26%, and the prevalence of vitamin D sufficiency (25(OH)D > 50 nmol/l) was 71%. The vitamin D status of the study groups is shown in table 9. The prevalence of severe vitamin D deficiency was not significantly different between the study groups. Most participants (70%) in both the schizophrenia and other psychoses groups had sufficient vitamin D status. In the group with non-psychotic depression, the prevalence of sufficient vitamin D status was 66%. There was no evidence to support differences in the mean 25(OH)D concentrations of the study groups. When standardizing the 25(OH)D concentrations to the vitamin D z-scores, as described above, the result was the same.

Table 9. Vitamin D status in the study groups of study I.

	Schizophrenia	Other psychoses	Non-psychotic depression	Controls	P-value
Serum 25(OH)D nmol/l					
Mean (95% CI)	65.5 (56.8, 74.2)	74.3 (59.8, 88.7)	65.3 (62.1, 68.4)	68.2 (67.4, 69.0)	0.23
Vitamin D z-score					
mean (95% CI)	-0.10 (-0.41, 0.21)	0.22 (-0.30, 0.73)	-0.11 (-0.22, 0.01)	0.00 (-0.03, 0.03)	0.28
Prevalence, <i>n</i> (%)					
< 30 nmol/l	1 (2.5)	0 (0.0)	11 (4.2)	149 (3.2)	
30–50 nmol/l	11 (27.5)	7 (29.2)	80 (30.3)	1 172 (25.2)	
≥ 50 nmol/l	28 (70.0)	17 (70.8)	173 (65.5)	3 338 (71.6)	

5.1.3 Correlation of the vitamin D score with anthropometric, lifestyle, socioeconomic, and psychiatric factors

We studied the correlation between vitamin D z-score and anthropometric, lifestyle, and socioeconomic factors as well as psychiatric treatment factors. In general, the correlation coefficients in the group with non-psychotic depression were of a similar magnitude and direction when compared to the control group. In the group with schizophrenia, a negative correlation between vitamin D and smoking status was found ($r = -0.37$, $p = 0.018$), while in the group with other psychoses, there was a positive correlation between vitamin D and smoking status ($r = 0.43$, $p = 0.034$). In the group with non-psychotic depression, a weak correlation between vitamin D and SEP was found ($r = 0.13$, $p = 0.04$). The correlations of these categorical variables were further assessed by analyzing the 95% CIs, and only the negative correlation between vitamin D and smoking status in the schizophrenia group remained significant.

5.2 Determinants and longitudinal changes in vitamin D status in middle-age (Study II)

5.2.1 Vitamin D status and longitudinal change from 1997 to 2012–2013.

We studied vitamin D status in the two follow-up timepoints using VDSP-calibrated values. In the study population ($n = 3\ 650$), the mean 25(OH)D

concentration was 54.2 nmol/l at 31 years and 64.8 nmol/l at 46 years. The mean change between the timepoints was an increase of 10.6 nmol/l. The prevalence of vitamin D deficiency (serum 25(OH)D < 50 nmol/l) decreased by half, from 43% to 24%. The seasonal fluctuation in vitamin D status was also found to decrease: the mean difference between the low and high vitamin D season was 17.2 nmol/l at 31 years and 8.3 nmol/l at 46 years. The monthly variation in serum 25(OH)D concentration between the timepoints is shown in figure 4.

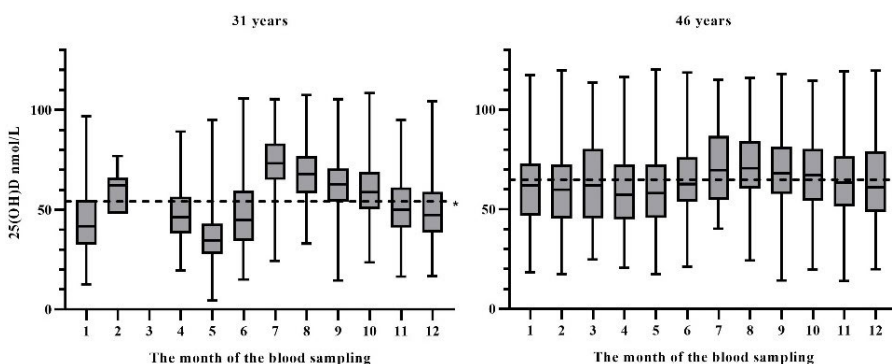


Fig. 4. Monthly variation in serum 25(OH)D concentrations at the age of 31 and 46. Reprinted under Creative Commons (CC BY) 4.0 license.

5.2.2 Vitamin D intake at the age of 46

The estimated dietary vitamin D intake was 11.0 µg/d (SD 5.8) in the study population at the age of 46 years. The intake from fortified dairy products was on average 6.0 µg/d, from fortified fat spreads 4.3 µg/d, and from fish 2.0 µg/d. When the dietary vitamin D intake was compared in the vitamin D status groups, the intake from total nutrition ($p < 0.001$), fortified dairy products ($p < 0.001$), and fish ($p = 0.027$) showed a decreasing trend towards the lowest vitamin D status group. The dietary intake of vitamin D from fortified fat spreads did not differ between the vitamin D status groups.

The dietary vitamin D intake between the sexes was different, with males gaining more vitamin D from their diet compared to females (12.3 µg/d and 10.1 µg/d, respectively). Specifically, males' intake from dairy products and fortified fat spreads (6.6 µg/d and 5.1 µg/d) was significantly higher than in females (5.6 µg/d and 3.7 µg/d). Meanwhile, intake from fish did not differ between the sexes (2.1 µg/d in males, 1.9 µg/d in females).

Vitamin D supplementation was used regularly by 19% and irregularly by 7% of the study population. Seventy-four percent reported no use of vitamin D supplementation. The use of supplementation was significantly more common in females compared to males. The median daily vitamin D dose from the supplement was 10.0 µg among those who had reported this information ($n = 866$). Vitamin D intake from different sources and by vitamin D status is shown in table 10.

Table 10. Vitamin D intake average and by vitamin D status at 46 years. Reprinted under Creative Commons (CC BY) 4.0 license.

Vitamin D intake	n	Mean ± SD	< 30 nmol/l	30–50 nmol/l	50–75 nmol/l	> 75 nmol/l	P-value
Total nutrition							
µg/d	3 638	11.0 ± 5.8	8.9 ± 18.7	9.6 ± 5.1	11.4 ± 6.1	11.6 ± 5.8	< 0.001
Fortified dairy products							
µg/d	3 555	6.0 ± 4.1	4.3 ± 3.9	5.0 ± 3.4	6.3 ± 4.4	6.6 ± 4.0	< 0.001
Fortified fat spreads							
µg/d	2 766	4.3 ± 2.6	4.4 ± 2.7	4.2 ± 2.5	4.4 ± 2.8	4.1 ± 2.5	0.054
Fish							
µg/d	3 384	2.0 ± 2.4	1.4 ± 2.0	1.8 ± 2.2	2.0 ± 2.4	2.2 ± 2.5	0.001
Vitamin D supplementation, % (n)	3 650						< 0.001
Regular		18.5 (672)	3.3 (3)	9.5 (73)	16.5 (288)	29.4 (310)	
Irregular		7.3 (268)	4.3 (4)	5.3 (40)	7.8 (135)	8.5 (89)	
No		74.2 (2 708)	92.4 (85)	85.2 (652)	75.7 (1 317)	62.1 (654)	
Supplementation dose							
µg/d, median (IQR)	866	10.0 (12.5)	4.4 (17.5)	10.0 (10)	10.0 (12.5)	16.3 (20.0)	< 0.001

5.2.3 Determinants of vitamin D status

The descriptive characteristics in vitamin D status groups at the ages 31 and 46 years are shown in table 11. When comparing the descriptive characteristics of the vitamin D status groups between the timepoints, we observed some differences. More blood sampling was conducted during the high vitamin D season at 31 years, whereas the opposite was found at 46 years. At the age of 31 years, the SEP differed significantly by vitamin D status, while there were more higher-level employees and fewer non-workers in the groups with 25(OH)D < 50 nmol/l compared to higher vitamin D status groups. However, difference in SEP attenuated in the next follow-up at 46 years. Higher BMI, lower physical activity, and high-risk alcohol consumption were more common in low vitamin D status groups at both timepoints.

Among these factors, the magnitude of the difference between the lowest and the highest vitamin D status group was larger at 46 years compared to 31 years. Also, being unmarried and smoking regularly were significantly more common among the lower vitamin D status groups at the age of 46 years.

Table 11. Descriptive characteristics in vitamin D status groups at 31 and 46 years¹. Reprinted under Creative Commons (CC BY) 4.0 license.

Status group	31 years (n = 3 541–3 650)				46 years (n = 3 462–3 650)				P-value
	< 30 (n = 346)	30–50 (n = 1 213)	50–75 (n = 1 581)	> 75 (n = 510)	< 30 (n = 92)	30–50 (n = 765)	50–75 (n = 1 740)	> 75 (n = 1 053)	
Females ² , % (n)	60.7 (210)	55.3 (671)	56.7 (897)	54.0 (276)	51.1 (47)	55.2 (422)	55.9 (972)	57.9 (610)	0.45
Marital status ² , % (n)									0.016
Married	75.4 (258)	75.1 (903)	75.0 (1 176)	74.1 (375)	73.3 (63)	75.3 (545)	79.4 (1 319)	81.0 (825)	
Unmarried	24.6 (84)	24.9 (300)	25.0 (391)	25.9 (131)	26.7 (23)	24.7 (202)	20.6 (343)	19.0 (193)	
SEP, % (n)									0.27
Higher-level employee	18.2 (59)	21.8 (258)	17.0 (261)	16.7 (83)	10.7 (9)	18.2 (131)	17.9 (295)	18.2 (184)	
Lower-level employee/entrepreneur	41.2 (134)	40.2 (475)	41.6 (640)	41.0 (204)	31.0 (26)	29.0 (209)	28.3 (467)	27.9 (282)	
Manual worker/farmer	30.2 (98)	27.1 (321)	27.4 (421)	28.1 (140)	52.4 (44)	46.0 (332)	49.6 (819)	48.8 (493)	
Not working	10.5 (34)	10.9 (129)	14.0 (215)	14.3 (71)	6.0 (5)	6.8 (49)	4.2 (70)	5.1 (52)	
BMI ³ , kg/m ²	24.6 ± 4.2	24.5 ± 4.0	24.6 ± 4.2	23.9 ± 3.4	27.9 ± 5.4	28.2 ± 5.5	26.8 ± 4.7	25.8 ± 4.2	< 0.001
Physical activity ^{3,4} , MET ⁵ hours/week, median (IQR)	10.2 (13.4)	10.9 (15.8)	11.9 (17.7)	12.9 (19.7)	10.1 (21.9)	11.9 (16.5)	13.1 (16.8)	15.6 (18.8)	< 0.001
Smoking ² , % (n)									< 0.001
Non-smoker	49.1 (168)	50.3 (601)	47.4 (740)	49.5 (251)	43.0 (37)	53.9 (387)	55.4 (914)	54.9 (554)	
Former smoker	26.3 (90)	25.3 (302)	27.5 (430)	26.4 (134)	20.9 (18)	25.8 (185)	26.9 (444)	29.6 (299)	
Current smoker	24.6 (84)	24.5 (293)	25.1 (392)	24.1 (122)	36.0 (31)	20.3 (146)	17.6 (291)	15.5 (156)	< 0.001

Status group	31 years (n = 3 541–3 650)			46 years (n = 3 462–3 650)			P-value
	< 30 (n = 346)	30–50 (n = 1 213)	50–75 (n = 1 581)	< 30 (n = 92)	30–50 (n = 765)	50–75 (n = 1 740)	
Alcohol consumption ^{2,6} , % (n)							
Abstainer	11.9 (40)	11.4 (134)	9.2 (140)	12.8 (11)	12.0 (87)	10.9 (182)	8.3 (85)
Low-risk drinker	83.8 (280)	84.5 (996)	85.6 (1 306)	68.6 (59)	78.4 (569)	82.1 (1 366)	85.0 (870)
High-risk drinker	4.2 (14)	4.2 (49)	5.2 (80)	18.6 (16)	9.6 (70)	7.0 (116)	6.7 (69)
Season of blood sampling ^{2,7} , % (n)							
High VitD season	24.9 (86)	39.5 (475)	77.5 (1 216)	13.0 (12)	26.3 (201)	44.7 (778)	51.4 (541)
Low VitD season	75.0 (260)	60.5 (728)	22.5 (354)	86.2 (81)	73.7 (564)	55.3 (962)	48.6 (512)
Latitude ^{2,8} , % (n)							
60°N	16.5 (57)	20.5 (249)	12.7 (201)	17.4 (16)	15.4 (118)	18.7 (325)	24.0 (253)
65°N	16.5 (57)	20.1 (244)	21.0 (332)	27.2 (25)	32.5 (249)	28.5 (496)	26.4 (278)
≥ 65°N	67.0 (232)	59.3 (719)	66.3 (1 048)	55.4 (51)	52.0 (398)	52.8 (919)	49.6 (522)

¹ Values are displayed as percentages with numbers in parentheses as % (n) or mean (SD) unless otherwise indicated, ² Differences between the groups were tested using Pearson's chi-squared test for categorical variables, ³ Differences between the groups were tested using one-way analysis of variance for normally distributed variables and the Kruskal–Wallis test for non-parametric continuous variables, ⁴ The MET physical activity scores in hours per week (frequency and duration of leisure time activities), ⁵ metabolic equivalent of task, ⁶ Alcohol intake: abstainer (0 g/d), low-risk drinker (males ≤ 40 g/d, females ≤ 20 g/d), and high-risk drinker (males > 40 g/d, females > 20 g/d), ⁷ High VitD season: summer (June 1–August 30) and autumn (September 1–October 31). Low vitamin D season: winter (November 1–March 31) and spring (April 1–May 31), ⁸ Latitude: 60°N, Helsinki and surrounding areas; 65°N, the city of Oulu; > 65°N, the northernmost provinces of Oulu and Lapland

In the linear regression model, the intake of fortified dairy products, the intake of fish, and regular vitamin D supplementation were positively associated with the vitamin D z-score at 46 years. The intake of fortified fat spreads was not associated with vitamin D z-score in the model. BMI was negatively associated with vitamin D z-score, while there was a positive association between vitamin D z-score at 46 years and earlier vitamin D status measured by the 31-year vitamin D z-score. The coefficient of determination (R^2) for the model was 0.16.

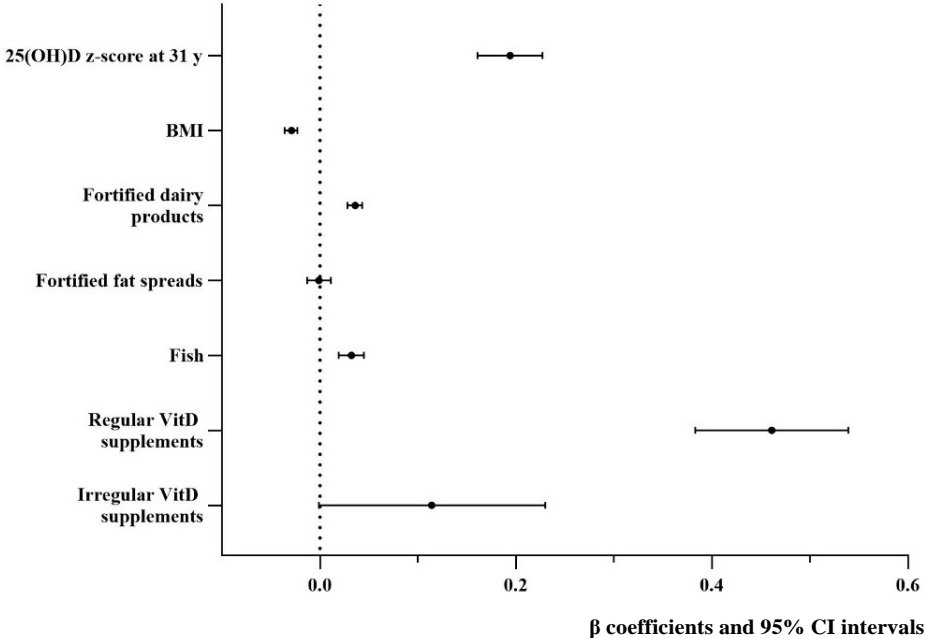


Fig. 5. The results of a multivariable linear regression of vitamin D z-score at 46 years with different exposures. For vitamin D supplementation, no supplementation was a reference category. Reprinted under Creative Commons (CC BY) 4.0 license.

5.3 Vitamin D status and multimorbidity (Study III)

5.3.1 Multimorbidity and related characteristics at the age of 46

The prevalences of the vitamin D status categories < 30 nmol/l, 30–50 nmol/l, 50–75 nmol/l, and > 75 nmol/l were 2.6%, 20.5%, 47.7%, and 29.2%, respectively. The descriptive characteristics in the vitamin D status categories (25(OH)D < 50 and ≥ 50 nmol/l) at the age of 46 years in this study population were essentially similar to those described in study II (chapter 5.2.3).

Among the study population ($n = 5\,514$), the prevalence of multimorbidity measured by CCI was 9.9%. The descriptive characteristics of the multimorbidity groups are presented in table 12. Vitamin D deficiency, defined as serum 25(OH)D < 50 nmol/l, was more common in the group with multimorbidity compared to the group with no morbidity. In the multimorbidity group, there were more females, participants with obesity, participants of lower SEP, and regular smokers.

Table 12. Descriptive characteristics for multimorbidity categories using CCI.

Characteristic	No morbidity ($n = 3\,779$; 68.2%)	Single morbidity ($n = 1\,190$; 21.5%)	Multimorbidity ($n = 546$; 9.9%)	P-value
VitD status				0.005
< 30 nmol/l, n (%)	81 (56.6)	41 (28.7)	21 (14.7)	
30–50 nmol/l, n (%)	748 (66.4)	244 (21.7)	135 (12.0)	
50–75 nmol/l, n (%)	1 834 (63.7)	560 (21.3)	236 (9.0)	
≥ 75 nmol/l, n (%)	1 116 (69.1)	345 (21.4)	154 (9.5)	
Latitude of residency				0.14
60°N, n (%)	1 658 (68.6)	509 (21.1)	250 (10.3)	
65°N, n (%)	899 (67.3)	289 (21.6)	147 (11.0)	
≥ 65°N, n (%)	1 222 (69.3)	392 (22.2)	149 (8.5)	
Sex				0.004
Females, n (%)	1 713 (70.3)	516 (21.2)	207 (8.5)	
males, n (%)	1 066 (67.1)	674 (21.9)	339 (11.0)	
SEP				< 0.001
higher-level employees, n (%)	730 (74.1)	176 (17.9)	79 (8.0)	
lower-level employees, n (%)	1 028 (69.3)	331 (22.3)	124 (8.4)	
farmers/manualworkers, n (%)	1 641 (67.1)	550 (22.5)	253 (10.4)	
non-workers, n (%)	94 (53.7)	46 (26.3)	35 (20.0)	
Physical activity				0.084
active, n (%)	1 022 (70.8)	296 (20.5)	126 (8.7)	
non-active, n (%)	2 524 (67.7)	826 (22.2)	379 (10.2)	

Characteristic	No morbidity (<i>n</i> = 3 779; 68.2%)	Single morbidity (<i>n</i> = 1 190; 21.5%)	Multimorbidity (<i>n</i> = 546; 9.9%)	P-value
Smoking,				< 0.001
non-smokers, <i>n</i> (%)	1 998 (71.7)	556 (19.9)	233 (8.4)	
previous smokers, <i>n</i> (%)	940 (66.5)	324 (22.9)	149 (10.5)	
regular smokers, <i>n</i> (%)	611 (62.0)	248 (25.2)	126 (12.8)	
Alcohol				0.12
low-risk user, <i>n</i> (%)	3 305 (68.8)	1 042 (21.7)	458 (9.5)	
high-risk user, <i>n</i> (%)	288 (65.8)	95 (21.7)	55 (12.6)	
BMI, kg/m ² mean (SD)	26.5 (4.4)	27.6 (5.6)	28.2 (5.8)	< 0.001
VitD supplementation				0.21
non-user, <i>n</i> (%)	2 796 (68.1)	909 (22.1)	401 (9.8)	
irregular, <i>n</i> (%)	276 (72.8)	71 (18.7)	32 (8.4)	
regular, <i>n</i> (%)	707 (68.6)	210 (20.4)	113 (11.0)	

5.3.2 Vitamin D status in single diseases of the CCI

When vitamin D status was investigated in the single diseases of the CCI, vitamin D deficiency was found to be significantly more common among participants with cerebrovascular disease, diabetes, and diabetes with complications. Also, in paraplegia and severe liver disease, the difference in vitamin D status was statistically significant, but the number of cases was low (*n* =13 in paraplegia, *n* = 2 in severe liver disease).

5.3.3 Association of vitamin D status and multimorbidity

In the ordinal logistic regression analysis, we observed a significant association between vitamin D status and multimorbidity in the non-adjusted model and models 1 and 2. In model 2, the OR for multimorbidity in vitamin D deficiency was 1.26 compared to vitamin D sufficiency (95% CI 1.10, 1.41). When adjusting with BMI in model 3, this association was attenuated (figure 6). The coefficient of determination (*R*²) for model 3 was 0.03.

When the logistic regression analysis was stratified by BMI using the cut-off of 30 kg/m², the observed association between vitamin D status and multimorbidity was non-significant in both strata. In the strata of BMI ≥ 30 kg/m², we observed a tendency towards an increased OR for multimorbidity in vitamin D deficiency in model 1 (OR 1.27; 95% CI 1.00, 1.63), but this association was attenuated when adjusting with SEP and lifestyle factors (model 2 OR 1.18; 95% CI 0.91, 1.55). In

the strata of BMI < 30 kg/m², there was no association between vitamin D deficiency and multimorbidity.

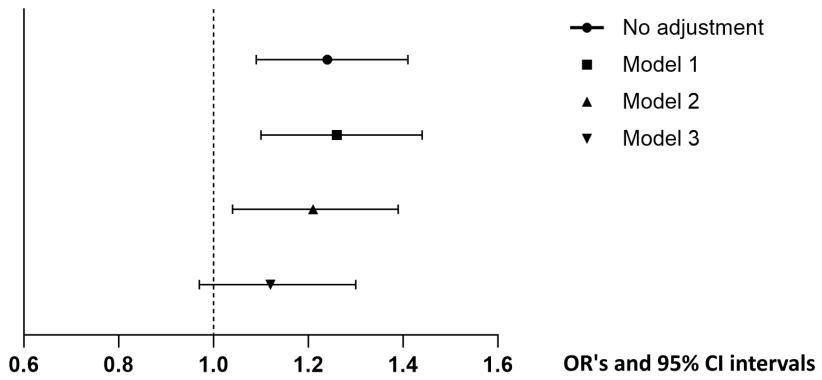


Fig. 6. ORs and 95% CIs of vitamin D deficiency for multimorbidity in the ordinal logistic regression models. For vitamin D status, 25(OH)D \geq 50 nmol/l was used as a reference category.

6 Discussion

This doctoral study investigated vitamin D status in a birth cohort sample using existing observational data from the NFBC1966. This study contributes to the literature on vitamin D status in adult populations with sufficient mean vitamin D status. As nutritional status has improved over the decades, the focus of vitamin D studies has shifted from vitamin D deficiency to understanding the meaning of vitamin D status in populations with sufficient vitamin D status. Although severe vitamin D deficiency and rickets are uncommon in developed countries nowadays, it is important to acknowledge the ability of this disorder to hamper musculoskeletal development, especially among risk groups, such as immigrant populations and institutionalized individuals with a limited diet. Additionally, groups with several risk factors, both behavioral factors, limited intake of vitamin D-rich sources, and obesity, seem to be at risk of vitamin D deficiency.

The findings from this thesis support the successful systematic vitamin D fortification of dairy products in the Finnish population and the regular use of vitamin D supplementation in the general population. Among most of the Finnish adult population, vitamin D status is sufficient according to the current knowledge, but individual factors, such as morbidity status, BMI, and socioeconomic background, also play an important role in vitamin D status in this setting.

The ethical considerations of this work pertain to the utilization of the NFBC1966 data. These data are handled using a high level of confidentiality and following the EU General Data Protection Regulation (679/2016) and Finnish Data Protection Act. The use of personal data is based on the cohort participants' written informed consent provided at their latest follow-up study. The use of existing data in a comprehensive manner is also considered ethical in terms of the effective use of resources.

In the following subchapters, I will discuss the findings of each study in more detail.

6.1 Vitamin D status and correlates of low vitamin D in schizophrenia, other psychoses, and non-psychotic depression (Study I)

In the first study, we examined vitamin D status in schizophrenia, other psychoses, and non-psychotic depression compared to a control population. Vitamin D status at 31 years in the NFBC1966 has been described previously in different settings

but not in relation to psychiatric disorders. In this study using a study population of young adults derived from a follow-up study of a birth cohort, we did not find significant differences in vitamin D status among the participants with psychiatric disorders and the controls. This result was observed based on serum 25(OH)D concentrations and a standardized vitamin D z-score. In general, vitamin D status among the control population was sufficient in 72% of the participants. Severe vitamin D deficiency (< 30 nmol/l) was also uncommon in the groups with schizophrenia, other psychoses, and non-psychotic depression (3%, 0%, and 4%, respectively).

This observation somewhat conflicts with previous knowledge, which has indicated vitamin D status to be lower in persons with depression and schizophrenia based on meta-analyzed results (Anglin et al., 2013; Belvederi Murri et al., 2013; Valipour et al., 2014; Zhu et al., 2020). However, this earlier body of evidence is heterogenous. The majority of the results regarding vitamin D status and schizophrenia are derived from inpatient populations, whereas, in the case of vitamin D status and depression, the data is largely representative of the findings in older adult populations. In this study, the groups with psychiatric disorders represented the outpatient population and had a relatively young age of 31 years. The sizes of the schizophrenia and other psychoses groups were relatively small, thus potentially limiting the power of the finding. However, the prevalences of schizophrenia and non-psychotic depression in this sample were 0.8% and 5.6%, which are close to previously reported number from Finland (0.8% for schizophrenia, 7.4% for depression) (Markkula et al., 2015; Perälä et al., 2007). The prevalence of all psychoses remained smaller than expected, 1.3% in this sample vs. 3.5% reported previously (Perälä et al., 2007).

When running the sensitivity analysis without exclusions for missing covariate information and only excluding pregnant women and lipid-lowering medication users, a significant difference in vitD status between the groups emerged. In these results, the mean concentration of 25(OH)D in the schizophrenia group was lower (62.9 nmol/l, $n = 47$) and in the other psychoses group higher (79.9 nmol/l, $n = 26$), while the means of the non-psychotic depression and control groups remained relatively stable. This finding should be considered with caution, since it was not standardized with important measurement-related factors, the season of blood sampling, the latitude of residency, and the technical covariate. Also, as mentioned, the sizes of the schizophrenia and other psychoses groups remained small.

The correlations between the serum 25(OH)D concentrations and anthropometric, lifestyle, and socioeconomic factors showed interesting

differences between the study groups. Reflecting the existing knowledge summarized earlier in this thesis, there was a significant negative correlation between vitamin D status and anthropometric measures, BMI, and WC in the control group. Yet, this finding was not evident in the groups with schizophrenia, other psychoses, and non-psychotic depression. A significant negative correlation between smoking and vitamin D status was found in the schizophrenia group as well as between socioeconomic position and vitamin D status in non-psychotic depression. However, the interesting picture from these results is that the correlations between the factors studied behaved differently in the controls vs. psychiatric disorder groups. This helps underline the complexity of studying vitamin D status, which is affected by several environmental factors and metabolic pathways.

It is of note that the NFBC1966 follow-up study at 31 years was conducted in 1997–1998, before the introduction of systematic food fortification with vitamin D in Finland (Lamberg-Allardt et al., 2006). It could be assumed that after the start of food fortification, vitamin D status among the participants with psychiatric disorders would have correspondingly increased, as it did among the general population sample in study II. The mean 25(OH)D concentrations measured in the 31-year follow-up study were relatively high in comparison to the Health 2000 survey conducted in Finland, which showed average serum 25(OH)D levels of 45.3 nmol/l (Jääskeläinen et al., 2017). This study population was characterized by older age (mean 51 years), a high prevalence of metabolic syndrome (43%), and blood sampling that occurred mainly during low vitamin D season, from September to March. Furthermore, the two studies used different vitamin D assays: a radioimmunoassay (RIA, Diasorin) was used in the Health 2000 survey to analyze serum 25(OH)D levels, while LC-MS/MS was used for the 31-year blood samples in the NFBC1966.

At the time of conducting these analyses, we did not have available data for harmonized 25(OH)D measurements. However, a harmonization procedure was previously conducted for NFBC1966 31-year samples, with the results showing that the concentrations measured by LC-MS/MS were higher compared to those measured by a RIA as well as constant variation with a mean difference of 32 nmol/l (Berry et al., 2017). The lack of harmonized data must be considered in the interpretation of the 25(OH)D concentrations in this study. However, the group comparisons have also been analyzed using standardized vitamin D scores, and this method diminishes the bias caused by the aforementioned analytical imprecision.

6.2 Determinants and longitudinal changes in vitamin D status in middle-age (Study II)

During the period between the follow-up studies, from 1997 to 2012–2013, vitamin D status in the Finnish adult population increased significantly, 10.6 nmol/l on average, after the start of systematic food fortification with vitamin D, which is in line with previous findings (Jääskeläinen et al., 2017). The 31-year 25(OH)D measurements were VDSP-calibrated for this study, which allowed for comparison with the later timepoint at 46 years as well as with other studies using 25(OH)D measurements standardized according to the VDSP. In addition to the increase in mean serum 25(OH)D concentrations, the prevalence of severe vitamin D deficiency (< 30 nmol/l) decreased from 9.5% to 2.5% and the prevalence of vitamin D deficiency (< 50 nmol/l) from 43% to 24% between the two timepoints. The highest increase in serum 25(OH)D concentrations was observed among participants with serum 25(OH)D < 30 nmol/l at the 31-year follow-up. On the other hand, we did not observe a significant increase in toxic 25(OH)D concentrations (> 250 nmol/l) after the start of food fortification ($n = 0$ at 31 years, $n = 2$ at 46 years among the total of 25(OH)D measurements). Wintertime vitamin D deficiency is a typical finding at northern latitudes (Webb et al., 1988), but after the start of food fortification, the mean difference between the low and high vitamin D seasons decreased from 17.2 nmol/l at 31 years to 8.3 nmol/l at 46 years. All these findings point to a successful public health action.

When conducting a comparison of this observed increase in vitamin D status with reports from other Nordic and developed countries, there are different findings. A study from Northern Sweden found no clear time trend in serum 25(OH)D concentrations from 1986 to 2014 (Summerhays et al., 2020), with similar observations made in Norway (Jorde et al., 2010), the Longitudinal Aging Study Amsterdam (van Schoor et al., 2014), and in three studies from the US (McKibben et al., 2016; Mirfakhraee et al., 2017; Schleicher et al., 2016), although substantial seasonal variation has been reported (Jorde et al., 2010; van Schoor et al., 2014). This might be due to differences in these countries' fortification policies, which have not been as systematic as in Finland.

A significant factor in the change in vitamin D status is the use of vitamin D supplementation. In this study, the use of regular vitamin D supplementation promoted an increase of 0.5 SD among regular supplement users compared to non-users. During the time between 31-year and 46-year follow-ups, the general knowledge of vitamin D supplementation has increased. This was also seen in the

results from Health 2000–2011, where vitamin D supplementation use increased from 11% in 2000 to 42% in 2011 (Jääskeläinen et al., 2017). In the current study, vitamin D supplementation was used by 26% of the studied population in 2012–2013, but, unfortunately, we did not have valid data from the 31-year study in 1997 to use for comparison. It should be noted that the postal questionnaire’s question about nutritional supplements was open-ended and not specifically inquiring about vitamin D supplementation, which may have led to underestimation of vitamin D supplementation use.

The average dietary vitamin D intake in the study population was 11.0 µg/d, which corresponds to the recommended intake level of Nordic nutrition guidelines (Itkonen et al., 2021). The principal source of dietary vitamin D in this study was fortified dairy products, constituting 6.0 µg of daily intake. The consumption of fortified dairy products as well as the consumption of fish were positively associated with vitamin D status in the final model. Vitamin D status increased on average 0.8 nmol/l per 1 µg of vitamin D from fortified dairy products and 0.6 nmol/l per 1 µg of vitamin D from fish. There might be potential to promote further improvement in vitamin D status by increasing the consumption of fish given the other beneficial effects of consuming fatty fish at recommended levels.

Interestingly, the vitamin D from fortified fat spreads was not associated with vitamin D status in this study. This could be due to the questions formulated for the postal questionnaire and the lower response rate compared to other nutrition questions ($n = 3\,638$ for dairy products, $n = 3\,555$ for fish, $n = 2\,766$ for fat spreads). However, the same finding was made in the Health 2000–2011 study (Jääskeläinen et al., 2017). Indeed, it has been suggested that the bioavailability of vitamin D in different fortified sources might be different (Grossmann & Tangpricha, 2010; Yang et al., 2013).

Vitamin D status is determined by multiple factors and seems to be linked to individual metabolic, behavioral, social, and genetic characteristics (Jääskeläinen et al., 2013; Wang et al., 2010). Often these factors are persistent, and it seems to be the same in the case of vitamin D status. In this study, we observed previous vitamin D status at 31 years to be predictive of current vitamin D status at 46 years. This is supported by an earlier finding regarding the tracking of serum 25(OH)D concentrations in a Norwegian study (Jorde et al., 2010). Future studies are needed to clarify this complex interplay between vitamin D status and multiple biopsychosocial factors.

6.3 Vitamin D status and multimorbidity (Study III)

In the third study, we investigated whether vitamin D status at the age of 46 years would predict multimorbidity at 54 years. An increased risk for multimorbidity measured by the CCI was observed in the vitamin D-deficient group, but the association was attenuated after adjusting for BMI. This seems consistent with previous knowledge about the confounding role of BMI in vitamin D status. In this study setting, BMI not only affects the risk for vitamin D deficiency but also the risk for multimorbidity. This is why we also wanted to test BMI as a modifying factor in the model using stratification.

Multimorbidity has not been described previously in the NFBC1966 using a validated multimorbidity measure. This sample, which had 25(OH)D measurements from the 46-year follow-up study and register data available, was characterized by a higher proportion of males, farmers and non-workers, regular smokers, and obese participants in the multimorbidity group compared to the groups with no morbidity or a single morbidity. When comparing the descriptive characteristics in the multimorbidity groups and vitamin D status groups, there seemed to be significant differences across several characteristics in the vitamin D status groups. Thus, vitamin D status could reflect several health-related characteristics even better than multimorbidity measured by the CCI.

Previous studies on the association of multimorbidity and vitamin D are limited, with only one study conducted in a Dutch adult population (Meems et al., 2015) and two in geriatric populations from Italy (Boccardi et al., 2019) and from Singapore (Moo et al., 2020). The previous evidence in the adult population also found lower concentrations of 25(OH)D to be associated with an increased prevalence of multimorbidity, even after adjusting for BMI (Meems et al., 2015). However, the multimorbidity measure used was different, with Meems et al. using a self-developed composite score including 12 disease domains. Regarding the studies among geriatric populations, the study conducted by Moo et al. used the CCI as a multimorbidity measure but did not find differences in 25(OH)D concentration in the multimorbidity groups (Moo et al., 2020). The study by Boccardi et al. found an association between vitamin D status and multimorbidity measured by the Cumulative Illness Rating Scale-Comorbidity Index (Boccardi et al., 2019). However, this study population had very low mean 25(OH)D concentrations, 26.5 ± 19.2 nmol/l, and were at a high risk of malnutrition, making this study population very different from a general population sample.

Regarding vitamin D status in those with single morbidities, vitamin D deficiency was significantly more common in participants with cerebrovascular disease, diabetes, and diabetes with complications. This is in line with previous findings from observational studies (Jani et al., 2021; Lips et al., 2017; Mohammadi et al., 2022; Zhang et al., 2017). However, RCTs and Mendelian randomization studies have not supported these observations (Bouillon et al., 2022).

The findings in the present study must be interpreted in the context of systematic vitamin D food fortification. This has been improving vitamin D intake and vitamin D status among the general population and might have weakened the possible association between vitamin D status and multimorbidity in the NFBC1966 population. Next, it would be informative to replicate this study in populations with lower vitamin D status.

To summarize the findings of this study, vitamin D deficiency was found to be associated with multimorbidity and might interfere with the course of accumulation of diseases, although this association seems to be confounded by BMI. Among middle-aged individuals with the risk of multimorbidity, especially those with obesity, vitamin D status should be considered by querying vitamin D intake or measuring 25(OH)D concentrations as a part of comprehensive clinical assessment. Even though there are several different confounding factors for vitamin D status, so far, there is no justification for leaving vitamin D deficiency uncorrected if observed (Bouillon et al., 2022).

7 Strengths and limitations

The study population in this thesis was from a large general population-based birth cohort with a high participation rate, including participants from a shared genetic, ethnic, and cultural background. Also, possible confounding by age was accounted for, as the birth cohort population were the same age. The population was also vitamin D-replete, as estimated by the mean 25(OH)D concentration. All these characteristics forms a solid base for an observational study of vitamin D status and its relationship to chronic conditions. The findings from this thesis can be generalizable to other populations from higher northern latitudes with generally sufficient vitamin D status, especially to other Nordic countries.

An important strength of this study was its use of 25(OH)D concentrations following the VDSP in studies II and III, allowing for interstudy comparability. We also used a standardization method for the 25(OH)D concentrations to account for vitamin D measurement-related variables.

Regarding disease information, there was the potential to combine comprehensive register data with the cohort data. Disease information from self-reports on the postal questionnaires was also discussed, but for methodological reasoning and comparability, the registers were chosen.

The comprehensive birth cohort data provided the opportunity to control for potential confounding factors influencing vitamin D status. It was also possible to evaluate vitamin D intake and supplementation use using the postal questionnaires, which contributed valuable information for study II.

A limitation of this thesis is the use of non-harmonized 25(OH)D measurements (*i.e.*, not calibrated according to the VDSP) in study I. However, the standardization removes this bias, making the comparison between the study groups accurate. Another limitation of study I is the limited sizes of the schizophrenia and other psychoses groups, which thereby limits the power of the study findings.

For estimating the longitudinal change in vitamin D status, it would have been informative to have more serum 25(OH)D measurement timepoints, such as a measurement before and after each wave of fortification. Also, having information about participants' supplementation use at age 31 would have made it possible to estimate the change in vitamin D supplementation and its effect on the change in vitamin D status between the two follow-up studies.

The study groups in studies I and III may have had a selection bias towards less severe cases of a disease (psychiatric disorders and multimorbidity), which

could affect the results. In the attrition analysis of the NFBC66, it was observed that participants in the follow-up study were more often females, married, having have children, employed, and from a higher SEP compared to non-participants (Nordström et al., 2022).

CCI was used as a multimorbidity measure, which has certain limitations, since it is originally developed to estimate 10-year mortality in breast cancer (Charlson et al., 1987). When studying middle-aged population, it could have been more justified to choose a functionality-based measure. However, we chose to use this measure, since it is widely used and a validated for several purposes (Charlson et al., 2022; Sundararajan et al., 2004). Also, it allows interstudy comparability.

8 Conclusions

This doctoral study aimed to contribute new knowledge about the change in vitamin D status in a research environment characterized by the initiation of systematic vitamin D food fortification. The study population was from a birth cohort sample representative of the general Finnish population, the participants of which aged from young adulthood to middle age during the follow-up period, and, thus, had an increasing incidence of chronic conditions with age.

During the follow-up from 31 to 46 years, vitamin D status improved significantly among the study population following the start of vitamin D food fortification. Before the start of fortification, there were no significant differences in vitamin D status between the groups with psychiatric disorders and the control population at 31 years. At 46 years, a higher risk for multimorbidity among participants with vitamin D deficiency was observed, although this association was confounded by BMI.

In conclusion, this study highlights an improvement in vitamin D status among the Finnish adult population and the determinants of vitamin D deficiency, like BMI, SEP, and morbidity burden, even among a generally vitamin D-replete population. Future studies are needed to help define the best procedure for locating vitamin D-deficient individuals among a generally vitamin D-replete population.

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List of original publications

- I Ikonen, H.*, Palaniswamy, S.*, Nordström, T., Järvelin, M. R., Herzig, K. H., Jääskeläinen, E., Seppälä, J., Miettunen, J., & Sebert, S. (2019). Vitamin D status and correlates of low vitamin D in schizophrenia, other psychoses and non-psychotic depression - The Northern Finland Birth Cohort 1966 study. *Psychiatry Research*, 279, 186–194. <https://doi.org/10.1016/j.psychres.2019.02.060>
- II Ikonen, H.*, Lumme, J.*, Seppälä, J., Pesonen, P., Piltonen, T., Järvelin, M. R., Herzig, K. H., Miettunen, J., Niinimäki, M., Palaniswamy, S., Sebert, S., & Ojaniemi, M. (2021). The determinants and longitudinal changes in vitamin D status in middle-age: a Northern Finland Birth Cohort 1966 study. *European Journal of Nutrition*, 60(8), 4541–4553. <https://doi.org/10.1007/s00394-021-02606-z>
- III Ikonen, H., Rautio, N., Miettunen, J., Sebert, S., & Seppälä, J. (2024). Vitamin D status and multimorbidity; a Northern Finland Birth Cohort 1966 study. Manuscript.

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Original publications are not included in the electronic version of the dissertation.

1806. Simula, Anna Sofia (2024) Trust your back : classification-based care for low back pain in primary care
1807. Salo, Heini (2024) Female urinary incontinence : work ability, hysterectomy as a risk factor and efficacy of invasive treatments
1808. Hautala, Maria (2024) Viral etiology and cytokine responses of infections leading to febrile seizures
1809. Haarala, Anna (2024) Atopic sensitization and associative factors of atopic diseases in the Northern Finland Birth Cohort 1966
1810. Molnár, Krisztina (2024) Factors affecting the quality of life and outcome after surgical treatment of cancer of the head and neck area
1811. Isosalo, Antti (2024) Medical image analysis and computing in breast cancer evaluation using mammography data
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1814. Kumpula, Timo (2024) The role of rare copy number variants and other candidate alleles in hereditary breast cancer susceptibility
1815. Ylimäki, Saija (2024) Laajavastuisen hoitotyön asiantuntijoiden näyttöön perustuvan hoitotyön osaaminen Suomessa ja Singaporessa
1816. Maikku, Mari (2024) Clinical screening of developmental dysplasia of the hip and longterm follow-up after early treatment
1817. Kuusela, Salla (2024) Association of family history of type I diabetes with autoimmunity and development of diabetes : family background of type I diabetes
1818. Karppanen, Anna-Kaisa (2024) Associations of early-life motor development, young adulthood temperament and anhedonia with physical activity in midlife and changes in physical activity during adulthood : Northern Finland Birth Cohort 1966
1819. Knuutila, Jarno (2024) Temporomandibular disorders in the Northern Finland Birth Cohort 1966 : the role of sociodemographic and health-related factors, pain sensitivity, genetics, and association with dental anxiety
1820. Hyrkäs, Pauliina (2024) Management of innovation activities in a public university hospital : characteristics, requirements, and influencing factors

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