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Abstract

There is limited knowledge available on the association of vitamin D with psychiatric disorders in young adults. We aimed to investigate vitamin D levels and associating factors in schizophrenia, other psychoses and non–psychotic depression. We studied 4,987 participants from the Northern Finland Birth Cohort 1966 (31 years) with available serum 25-hydroxyvitamin D [25(OH)D] measurements. The final sample was divided into four groups: schizophrenia (N=40), other psychoses (n=24), non-psychotic depression (n=264) and control (n=4,659). To account for the influence of environmental and technical covariates, we generated a vitamin D score variable with correction for season, sex, batch effect and latitude. We further examined how vitamin D levels correlate with anthropometric, lifestyle, socioeconomic and psychiatric measures. Neither serum 25(OH)D concentration nor vitamin D score differed between schizophrenia, other psychoses, non-psychotic depression and control group. The prevalence of vitamin D deficiency was 3.2%, insufficiency 25.5%, and sufficiency 71.3%. Low vitamin D score correlated with regular smoking in the group with schizophrenia. No difference was observed in other psychiatric conditions. We did not find any difference in vitamin D status between schizophrenia, psychoses, non-psychotic depression and control groups, but future studies are warranted to elucidate the role of vitamin D in psychiatric conditions.

Keywords	vitamin D, schizophrenia, other psychoses, non–psychotic depression, 25(OH)D.

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There are no linked research data sets for this submission. The following reason is given:
Data will be made available on request

Highlights

- Data was collected from a large homogeneous Northern Finland Birth Cohort 1966.
- Vitamin D score adjusting for season, latitude, sex and batch effect was used.
- Vitamin D did not differ between psychoses, depression and controls.
- Vitamin D and smoking had a moderate negative correlation in schizophrenia.
- Vitamin D did not correlate with other lifestyle, socioeconomic and psychiatric factors.

Abstract

There is limited knowledge available on the association of vitamin D with psychiatric disorders in young adults. We aimed to investigate vitamin D levels and associating factors in schizophrenia, other psychoses and non–psychotic depression. We studied 4,987 participants from the Northern Finland Birth Cohort 1966 (31 years) with available serum 25-hydroxyvitamin D [25(OH)D] measurements. The final sample was divided into four groups: schizophrenia (N=40), other psychoses (*n*=24), non-psychotic depression (*n*=264) and control (*n*=4,659). To account for the influence of environmental and technical covariates, we generated a vitamin D score variable with correction for season, sex, batch effect and latitude. We further examined how vitamin D levels correlate with anthropometric, lifestyle, socioeconomic and psychiatric measures. Neither serum 25(OH)D concentration nor vitamin D score differed between schizophrenia, other psychoses, non-psychotic depression and control group. The prevalence of vitamin D deficiency was 3.2%, insufficiency 25.5%, and sufficiency 71.3%. Low vitamin D score correlated with regular smoking in the group with schizophrenia. No difference was observed in other psychiatric conditions. We did not find any difference in vitamin D status between schizophrenia, psychoses, non-psychotic depression and control groups, but future studies are warranted to elucidate the role of vitamin D in psychiatric conditions.

Keywords: vitamin D, schizophrenia, other psychoses, non–psychotic depression, 25(OH)D.

Vitamin D status and correlates of low vitamin D in schizophrenia, other psychoses and non–psychotic depression – The Northern Finland Birth Cohort 1966 study

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1. Introduction

In recent years, research investigating the influence of vitamin D in neuropsychiatric diseases has increased rapidly. Vitamin D receptor is widely expressed in human brain being most abundant in the hypothalamus and substantia nigra (Eyles et al., 2005). Vitamin D has been reported to regulate multiple neurotransmission pathways both in regional and general level, including dopamine, serotonin, noradrenalin and glutamine (Kesby et al., 2017). For example, prenatal vitamin D has found to regulate tyrosine metabolism and thereby dopaminergic pathways (Cui et al., 2015). Neuroprotective effects of vitamin D have been established *in vitro*, for example in inhibiting the synthesis of tumor necrosis factor-alpha and interleukin-6 (Lefebvre d'Hellencourt et al., 2003). Therefore, it is not surprising that low vitamin D concentrations have been associated with neuropsychiatric disorders like Alzheimer disease, autism spectrum disorders, depression and schizophrenia (Groves et al., 2014). The dysregulation of dopaminergic pathways has been linked to schizophrenia for decades and recent animal models strengthen the idea that developmental vitamin D is protecting from abnormal dopaminergic phenotypes (Luan et al, 2018). Novel findings indicate a role of glutaminergic dysfunction and inflammation in the pathogenesis of both schizophrenia and depression (Yang and Tsai, 2017,Gerhard et al., 2016).

A systematic review and meta-analysis using ten cross-sectional studies has reported a 1.31-fold (95% confidence intervals (CI): 1.00 –1.71) increased odds ratio (OR) of non–psychotic depression in individuals being in the lowest *vs*. the highest vitamin D category (Anglin et al., 2013) in mainly non-clinical samples. However, most of the studies included in this meta–analysis were conducted in older adults (Anglin et al., 2013). Regarding schizophrenia, the body of evidence on vitamin D and schizophrenia was summarised in a systematic review and meta-analysis, in which 19 observational studies were included (Valipour et al., 2014). The mean difference in serum 25-hydroxyvitamin D [25(OH)D] between schizophrenia patients and control participants was −14.8 nmol/l (95% CI: −26.7, −2.85) and vitamin D deficient subjects had OR 2.16 (95% CI: 1.32, 3.56) for having

schizophrenia compared to vitamin D sufficient subjects (Valipour et al., 2014). However, in this meta-analysis more than a half of the participants were inpatients (*n*=780/1442), which may result in heterogeneity in the interpretation of the results in comparison with the non-hospitalised individuals (Valipour et al., 2014). There is a vast amount of heterogeneity in the studies included in the systematic reviews and meta-analyses which investigated the association between 25(OH)D and non–psychotic depression, schizophrenia and psychotic disorders (Anglin et al., 2013,Valipour et al., 2014,Adamson et al., 2017).

Higher vitamin D concentration has been associated with several positive health and behavioural characteristics: young age, normal weight, healthy diet, physical activity, time spent outdoors (Forrest and Stuhldreher, 2011). On the contrary, a large meta-analysis has reported lower vitamin D status and its association with all-cause and cause-specific mortality in older population (Schottker et al., 2014). A well–known observation is that depression and schizophrenia patients have an increased risk of mortality and they are less likely to adopt a healthy lifestyle (De Hert et al., 2011), which increases their risk for inadequate vitamin D intake. Patients with depression and schizophrenia tend to be more sedentary and physically less active than general population, which predisposes them to inadequate ultraviolet-B (UV–B) radiation for vitamin D synthesis (Helgadottir et al., 2015,Stubbs et al., 2016). The dietary patterns of depression and psychosis patients are also unhealthier compared to healthy controls, which increases the likelihood to fall below the recommended dietary intake of vitamin D (Hahn et al., 2016,Yu et al., 2014). Against this background we can understand the complexity of studying vitamin D especially in the subjects with depression and psychosis where reverse causation remains to be elucidated. Potential confounders in vitamin D studies are the season and the geographical location (Holick, 2007,Mithal et al., 2009). Summer season accounts for 80% of natural vitamin D synthesis (Holick, 2007,Mithal et al., 2009,Huotari and Herzig, 2008), and the serum 25(OH)D concentration is influenced by the latitude as well as the season of the year.

In the light of the current knowledge, we investigated serum 25(OH)D status in individuals with schizophrenia, other psychoses and non–psychotic depression in a cohort of young adults from the northern latitudes. In comparison to the earlier studies in the field, the study population is characterised by its young age, the inclusion of both inpatients and outpatients and the use of diagnostic registers. Another aim was to study correlations between vitamin D and anthropometric, lifestyle, socioeconomic and psychiatric factors, since this is a topic with scarce evidence.

2. Material and methods

2.1. Study population

We analysed the data from a prospective birth cohort study, the Northern Finland Birth Cohort 1966 (NFBC1966). The study recruited all pregnant women living in Northern Finland (provinces of Oulu and Lapland) with expected delivery dates in 1966. The cohort included 12,058 live born children. The complete details of the study have been published elsewhere (Rantakallio, 1988). The data used in this study is based on the 31–year follow-up conducted in 1997. Information on somatic and mental health, medications as well as socioeconomic status was collected using a postal questionnaire and this was returned by 75% (*n*=8,767). At the same time, those living at the original target area (Northern Finland), or in the capital (Helsinki) area were invited to a clinical examination, in which 71% (*n*=6033) participated (Jarvelin et al., 2004). The flowchart of the study population is shown in **Figure 1**. The participants gave written informed consent. The study was approved by the ethical committee of the Northern Ostrobothnia Hospital District and University of Oulu. The procedures follow the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Exposure/explanatory: For the current study, we included only participants with available vitamin D measurements and without missing information from the covariates studied (**Figure 1**). The final sample consisted of 4,987 participants with following categories: depression [*n*=264 (5.3%)], schizophrenia [*n*=40 (0.8%)], other psychoses [*n*=24 (0.5%)] and control [*n*=4,659 (93.4%)]. The

diagnoses were collected using Care Register for Health Care (inpatient treatments until 2013), Finnish outpatient registers (specialised care 1998–2013, primary care 2011–2013), Finnish Center for Pensions (disability pensions until 2013), and Social Insurance Institution registers (reimbursable medicines until 2005 and, disability pensions until 2000 and sick days until 1999). The diagnosis codes used are based on International Statistical Classification of Diseases and Related Health Problems (ICD): ICD–8 (until 1986), ICD–9 (1987–1995) and ICD–10 (since 1996). Codes 2960, 2980, 3004, 7902 (ICD–8), 2961, 3004 (ICD–9) and F32 (except F323), F33 (except F333), F341, F3810 (ICD–10) were used for non-psychotic depression diagnosis. Codes 2950–2959, 297 (ICD–8), 2950–2959, 297 (ICD–9) and F20, F22, F24, F25 (ICD–10) were used for schizophrenia diagnosis. Other psychoses group includes subjects with diagnosed affective psychosis, brief reactive psychosis and not otherwise specified psychosis. Codes 2960-2969, 2980-2983, 2988, 2989, 299 (ICD-8), 2962E-2964E, 2967, 2961E, 2988, 2989 (ICD–9) and F23, F28, F29, F302, F312, F315, F323, F333 (ICD–10) were used for other psychoses group. Substance-induced and organic psychoses were not included in the study because of their different etiology.

2.2. Covariates

The season of blood sampling: Participants' attendance during clinical examination was used to calculate the season of blood sampling. According to the Finnish Meteorological Institute, season was categorized as summer (June – August), autumn (September – October), winter (November – March) and spring (April – May) (Finnish Meterological Institute, 2018).

Latitude: Participants' residence at 31 years was collected from population register and was categorised as residing in the city of Oulu (65°N), other northernmost provinces of Oulu and Lapland (>65°N), or in the city of Helsinki (60°N).

Anthropometric measures: During clinical examination, height (cm), weight (kg) and waist circumference (WC, cm) were measured from participants with light clothing by well–trained nurses.

BMI (kg/m^2) was calculated from height and weight. BMI was further categorised as <25 kg/m^2 and ≥ 25 kg/m^2.

The following variables were calculated based on the responses in the postal questionnaire. Socioeconomic status (SES) was classified as professionals and skilled workers (category I) and unskilled workers, farmers and others (pensioner, student, long-term unemployed or not defined) (category II). Smoking status was categorized as non-smoker, occasional/former smoker and active smoker. Alcohol intake was calculated as grams per day (g/day) based on the consumption of beer, wine and spirits during six months before the questionnaire(Laitinen et al., 2004). Diet score was calculated based on the daily consumption of red meat, sausages, crisp or rye bread, vegetables, berries or salads, six months prior to the questionnaire. The score ranged from 0-5 where score <3 indicates a healthy and points 4–5 an unhealthy diet consumption. An unhealthy diet is daily or almost daily consumption of sausages and less consumption of rye bread, vegetables and fruits (Laitinen et al., 2004). Physical activity was calculated based on the reported leisure and brisk physical activity and was presented as metabolic equivalent of task (MET) scores in hours per week(Suija et al., 2013). Method of contraception in females was categorised as no contraception, oral contraceptive pills and other kind of contraception(Morin-Papunen et al., 2008). Similarly, the use of medication was collected from the questionnaire based on the responses for the present medication and their dosage as prescribed by the doctor. Postal questionnaire data versus pharmacy data for psychoactive medication has been estimated previously in this cohort and was considered methodical to use in the studies(Haapea et al., 2010).

The age of onset of the disease was determined as the first registered depression or psychosis episode. Psychiatric treatment days were collected from the Care Register for Health Care and defined as a day of hospital inpatient care because of a psychiatric diagnosis.

2.3. Vitamin D measurement

Blood samples were drawn between 8 a.m. and 11 a.m. preceded by an overnight fast as part of the clinical examination at 31 years. Serum concentrations of $25(OH)D_2$ and $25(OH)D_3$ were determined using a high-performance liquid chromatography-tandem mass spectrometry in four batches. Serum 25(OH)D concentration was defined by the sum of $25(OH)D_2$ and $25(OH)D_3$. The detailed assay procedure is described elsewhere (Williams et al., 2016). Vitamin D status was classified according to Institute of Medicine criteria (IOM, 2010) as ≤30 nmol/l (deficient), 20-50 nmol/l (insufficient) and ≥50 nmol/l (sufficient) (Ross et al., 2011).

2.4. Vitamin D score

The serum 25(OH)D status in the NFBC1966 has been reported to be determined by sex, the season of blood sampling, the latitude of residence and technical covariates as reported by Palaniswamy et al., (2017) (Palaniswamy et al., 2017) (**Table 2**). All these factors should be considered in order to control for the influence of the factors on the vitamin D status of an individual. Therefore, vitamin D score variable taking into account adjustment for the season of blood sampling, the latitude of residence, batch and sex was computed (**Supplementary Table 1**). We then investigated the correlations between vitamin D score and anthropometric, lifestyle, socioeconomic and psychiatric factors in schizophrenia, other psychoses, non–psychotic depression and control group.

2.5. Statistical analyses

The differences across the four groups were calculated using Pearson's Chi–square test and Kruskal–Wallis test. The mean differences in serum 25(OH)D concentration and vitamin D score across the groups were examined by one-way ANOVA. The serum 25(OH)D measurement was examined as quintiles using the quintile cuts for the 20^{th}, 40^{th}, 60^{th} and 80^{th} percentiles. The differences in 25(OH)D quintiles between controls versus schizophrenia and other psychoses were examined using Fischer's exact test. For the difference in quintiles between controls and non-psychotic depression we used

Chi–squared test. The vitamin D score was then used on the standardised scale, z–score [mean=0, standard deviation (SD)=1]. The correlations of vitamin D z–score variable with anthropometric (BMI, WC) and lifestyle variables (smoking, physical activity, alcohol, diet), socioeconomic status (SES) and psychiatric treatment days were examined using Pearson's Correlation for normally distributed variables and Spearman's rho for categorical variables. Statistical significance was set at $p<0.05$ (two–sided). All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Characteristics of the study population

The characteristics of the study groups are presented in **Table 1**. The cohort included a total of 4,987 subjects: 40 with schizophrenia, 24 with other psychoses, 264 with non-psychotic depression and 4,659 control participants. The groups differed in location, BMI and WC, SES, psychiatric treatment days and in the use of antipsychotic and antidepressant medication (p=0.01). In the group with schizophrenia the largest proportion of subjects was living in rural areas compared to other groups (75.0%) and the least proportion in the capital region (5.0%). The greatest percentage of the capital region residents was found in the group with depression (22.7%). The mean BMI (26.2 *vs*. 24.6 kg/m^2, p=0.01) and WC (91.9 *vs*. 83.6cm, p=<0.01) in the group with schizophrenia were higher than in the control group. In addition, the mean BMI in the group with non–psychotic depression was significantly higher compared to control group (25.2 *vs*. 24.6kg/m^2, p=0.02). The percentage of professional and skilled workers was lower in the group with schizophrenia (5.0%) compared to other groups. The mean number of lifetime psychiatric treatment days was the highest in the group with schizophrenia (92.5), followed by the group with other psychoses (29.5). In addition, the use of antipsychotics was higher in the group with schizophrenia and other psychoses compared to others

(40.6% and 26.7%, respectively), while the group with non–psychotic depression had the largest percentage of antidepressant users (9.2%).

3.2. Serum 25(OH)D status and vitamin D score in the study population

The vitamin D status of the study population is shown in **Table 2**. Mean serum total 25(OH)D was 65.5 nmol/l in the group with schizophrenia, 74.3 nmol/l in the group with other psychoses, 65.3 nmol/l in the group with non–psychotic depression and 68.2 nmol/l in the control group (p=0.23). When using the 25(OH)D quintiles, no differences between the groups were observed (**Supplementary table 2 and 3**). The differences between the groups remained the same in vitamin D score when adjusting with the season of blood sampling, latitude and batch **(Figure 2)**. The vitamin D scores (95% CI) were −0.10 (−0.41, 0.21) in the group with schizophrenia, 0.22 (−0.30, 0.73) in the group with other psychoses, −0.11 (−0.22, 0.01) in the group with non-psychotic depression and 0.00 (−0.03, 0.03) in the control group (p=0.28). In addition, when the model was adjusted for sex, we obtained similar results (**Supplementary table 1**).

Since the sizes of schizophrenia and other psychoses groups were small, we made a supplementary analysis comparing vitamin D in the total population with only excluding pregnant women and the users of lipid lowering medication users (**Supplementary table 4**). The analysis yielded significant results with wide confidence intervals with 25(OH)D concentration and being the lowest in schizophrenia and the highest in other psychoses group [62.9 nmol/l (95% CI: 55.3, 70.5) and 79.9 nmol/l (95% CI: 64.3, 95.5), respectively, p=0.03].

According to Institute of Medicine (2011) cutoffs the prevalence of vitamin D deficiency [serum 25(OH)D<30 nmol/l] was 3.2% and the prevalence of vitamin D insufficiency [25(OH)D 30-50 nmol/l] was 25.5% in the study population (n=4,987) (**Table 3**). 71.3% of the population was vitamin D sufficient [25(OH)D>50 nmol/l].

Table 4 shows the vitamin D status in schizophrenia, other psychoses, non–psychotic depression and control individuals (IOM, 2010). The prevalence of vitamin D deficiency [serum 25(OH)D<30 nmol/l] was 2.5% and 4.2% in the group with schizophrenia and non–psychotic depression. The prevalence of vitamin D insufficiency [25(OH)D 30–50 nmol/l] was 27.5%, 29.2% and 30.3% in the group with schizophrenia, other psychoses and non–psychotic depression, respectively. Vitamin D sufficiency (>50 nmol/L) was 70% in both the group with schizophrenia and other psychoses and 65.5% in the group with non–psychotic depression.

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

Table 5 shows the results for correlation coefficients between vitamin D z–score and anthropometrics (BMI, WC), lifestyle factors (physical activity, diet, smoking, alcohol), SES and psychiatric treatment days. The correlation coefficients in the group with non–psychotic depression was of similar magnitude and direction when compared to the control group. In the group with schizophrenia, a negative correlation between vitamin D and smoking was found (r=−0.37, p=0.018) and in the group with other psychoses, a positive correlation between vitamin D and smoking was observed (r=0.43, p=0.034). When the correlations of the categorical variables were further assessed by checking their means and 95% CI's, only the negative correlation in the group with schizophrenia remained. In regular smokers of the group with schizophrenia the mean vitamin D score was −0.44 (95% CI: −0.81, −0.08). In the group with non–psychotic depression a weak correlation between vitamin D and SES was found (r=0.13, p=0.04).

4. Discussion

4.1. Vitamin D status in the study population

In this study we found no differences in serum 25(OH)D between schizophrenia, other psychoses, non-psychotic depression and control groups. Our study included adjustment with important

220 confounders and consisted of population–based sample of young adults. Compared to general vitamin
221 D status in Finnish population our study population tended to have higher serum 25(OH)D
222 concentration at 31 years. The mean serum 25(OH)D concentrations were 65.5, 74.3, 65.3 and 68.2
223 nmol/l in the group with schizophrenia, other psychoses, non–psychotic depression and controls,
224 respectively. Serum 25(OH)D concentration measured in the study was before the introduction of
225 food fortification with vitamin D in Finland (1997). In the Health 2000 survey conducted in Finland,
226 which is the nearest time–point for comparison with our study population, the average serum
227 25(OH)D was 45.3 nmol/l (Jaaskelainen et al., 2013). However, the mean age of the study population
228 was 51 years, 43% of the study population had metabolic syndrome and most of the samples were
229 taken between September and March, also in low vitamin D months (Jaaskelainen et al., 2013).

230 We used a vitamin D z–score, taking into consideration the effect of environmental and technical
231 factors influencing vitamin D as previously described in Palaniswamy *et al*., 2017 (Palaniswamy et
232 al., 2017). The vitamin D score variable showed no difference across the groups similar to the serum
233 25(OH)D concentrations. However, the mean concentration varied marginally with wider confidence
234 intervals when comparing to the control group. The supplementary analysis comparing vitamin D
235 across the groups using only mandatory exclusion criteria (**Supplementary table 4**) showed a
236 statistically significant difference between the study groups, but we consider this with caution, since
237 the data is unadjusted and the difference might be explained by the seasonal variation of the blood
238 sampling, differences in geographical location and in technical covariates.

239 A recent study conducted in Danish population studied the association of neonatal vitamin D and
240 schizophrenia using a quintile approach (Eyles et al, 2018). They found a significantly increased risk
241 of schizophrenia in the lowest vitamin D quintile compared to the reference quintile. We used the
242 same quintile approach in our study population, since this might be more informative when studying
243 small groups. However, we found no differences between the groups. We must consider the young
244 age of our study population at 31-year follow-up and less severe course of the disease among the

study participants. In addition, Eyles et al has studied the role of developmental vitamin D, which seems to have a crucial role in the brain development. Our study is focusing in the role of vitamin D in later life, which is more unclear and might be linked to lifestyle factors and overall health status.

4.2. Vitamin D status in the group with schizophrenia

In the present study, serum 25(OH)D tended to be lower in the group with schizophrenia than in the control group. However, this finding was not statistically significant. A meta–analysis on vitamin D and schizophrenia reported a significant difference in serum vitamin D between schizophrenia patients and controls (Valipour et al., 2014). This difference was only observed in inpatients, not in outpatients (Valipour et al., 2014). Another study based on Turkish population (mean age=39 years) reported a significant difference in median serum 25(OH)D between acute episode schizophrenia, remission patients and controls (17.9 nmol/L, 37.5 nmol/L and 37.5 nmol/, respectively, p <0.001) (Yuksel et al., 2014). This finding is also supporting the difference between vitamin D in inpatients and outpatients. Our study was performed in younger adults and had higher serum 25(OH)D concentration compared to the previous investigation (Yuksel et al., 2014). In addition, the present study used a non-clinical sample drawn from the general population, which is more likely to have less psychiatric hospitalisations and positive symptoms than non–participants (Haapea et al., 2007). In line with our results, a recently published Mendelian Randomization study has examined the causal association of serum 25(OH)D concentration with schizophrenia (Taylor et al., 2016). This study based on summary data of genome-wide association studies of 34,241 schizophrenia cases and 45,604 control failed to support a causal association and 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). Altogether the body of evidence linking vitamin D status and schizophrenia remains contradictory and support that other pathways could explain the results of meta–analyses of observational studies, especially in the inpatient groups. There are also clues that vitamin D might be associated with different expression of schizophrenia

symptoms. A recent study found depression and anxiety to be more common in schizophrenia patients with hypovitaminosis D (Fond G et al., 2018).

4.3. Vitamin D status in the group with other psychoses

Studies on vitamin D and psychosis are mainly conducted in schizophrenia patients, but a mini meta–analysis (seven studies) about vitamin D and psychosis included also other psychotic disorders (Belvederi Murri et al., 2013). No difference in vitamin D was observed between the group with other psychoses and control participants in the meta–analysis, which is in line with our findings (Belvederi Murri et al., 2013). In addition, the study compared vitamin D status in the group with schizophrenia and other psychoses: here a trend towards lower vitamin D in the group with schizophrenia was found, but the finding was not significant (Belvederi Murri et al., 2013). Similar results were observed in the present study comparing the group with schizophrenia *vs*. other psychoses.

4.4. Vitamin D status in the group with non–psychotic depression

The meta–analysis and systematic review on vitamin D in depression, also referred to earlier, reported an increased risk of non–psychotic depression in the lowest versus the highest vitamin D category (Anglin et al., 2013). However, four of the cross–sectional studies included in this meta–analysis had unrepresentative samples and other seven studies reported risk using self-reported psychiatric rating scales (Anglin et al., 2013). In the present study, we used register–based diagnoses, which is also different from the studies of the meta–analysis (Anglin et al., 2013), and we found no difference between non-psychotic depression and control group.

4.5. Correlation of vitamin D score with anthropometric, lifestyle, socioeconomic and psychiatric factors

Lower vitamin D levels in psychiatric patients have been explained for example by lifestyle factors predisposing to vitamin D deficiency: less time spent outdoors, poorer diet, higher rate of obesity and smoking (Jaaskelainen et al., 2013). In the present study, the groups did not differ in the lifestyle factors despite higher BMI and WC being more common in the group with schizophrenia. In addition,

294 a moderate negative correlation between vitamin D and smoking was found in the group with
295 schizophrenia. No differences in correlations between other psychiatric groups and lifestyle factors
296 were observed in the present study.

297 4.6. Strengths and limitations

298 The strength of our study is a coherent study population of same, relatively young age from a
299 genetically homogenous district of Northern Finland. Latitude and season have shown to influence
300 the cutaneous production of vitamin D (D3) already in the 1980s (Webb et al., 1988). In addition,
301 skin pigmentation, living conditions and cultural practices, e.g. clothing, affect vitamin D status,
302 which makes interpretation of vitamin D studies even more difficult. However, the present study
303 population comes from the same ethnic background, geographical area and culture. We studied
304 comprehensively the association of vitamin D in individuals with schizophrenia, other psychoses and
305 non–psychotic depression. The diagnoses are based on well-documented, nationwide register data.
306 Different from most of earlier studies, we used vitamin D score with correction for environmental
307 and technical factors for better evaluation of the differences between the groups as well as correlation
308 coefficients to study possible causes of these differences.

309 The limitation of our study is the relatively high attrition of subjects with psychoses (23% in males;
310 8% in females) and non–psychotic disorder (23% in males; 9% in females) at the 31–year follow up
311 (Haapea et al., 2008). This is indicating that subjects with psychiatric symptoms, but not yet
312 diagnosed, were less likely to participate than non–symptomatic controls, even though this is a
313 common phenomenon when studying psychiatric disorders. Cohort members attending the follow–
314 up study tend to be healthier and outpatients, so cases with more severe non–psychotic depression or
315 psychosis may be underrepresented, and we are more unlikely to see differences between the groups.
316 Also, selection bias towards less severe cases of the disease might affect our results. This has been
317 studied previously in subjects with established psychosis in NFBC1966 cohort population (Haapea et
318 al., 2007). The data did not include information on symptom severity scales, but as stated above, we

have the information that in general, the participants of the cohort study are more likely to have less positive symptoms and less psychiatric hospitalisations compared to non-participants (Haapea et al., 2007). The sizes of schizophrenia and other psychoses groups were small, so the power of the study is limited. In addition, our study population was of younger age (31 years) when compared to previous investigations. Unfortunately, the data did not include adequate information on vitamin supplementation used, which would have provided additional information. However, we know that national recommendation for vitamin D supplementation was launched in Finland in 2002, which is after the follow–up study at 31 years was conducted. In Health 2000 survey the use of vitamin D supplementation was 10% at that time, so before year 2002 the use of vitamin D supplements was not common in Finland (Jaaskelainen et al., 2013).

In conclusion, our findings support the idea that in outpatient population of NFBC1966 there are no differences in serum 25(OH)D and vitamin D score between the groups with schizophrenia, other psychoses, non–psychotic depression and controls. We observed that low vitamin D correlates with regular smoking in the group with schizophrenia. The study warrants replications of the results in large population samples. Our intended follow–up study from NFBC1966 at 46 years may provide additional information on the vitamin D status in psychiatric conditions in the future.

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Contributions: HI, SP, JS, JM and SS designed the analysis. SP performed the statistical analyses. HI and SP contributed equally in the writing of the manuscript with guidance from JS, JM, TN, EJ and SS. MRJ, JM, and KHH were responsible for data collection of variables and blood sampling related to this analysis. All authors contributed intellectually to the manuscript and approved the final version.

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FIGURES:

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Figure 1. Flowchart of the study population in NFBC1966

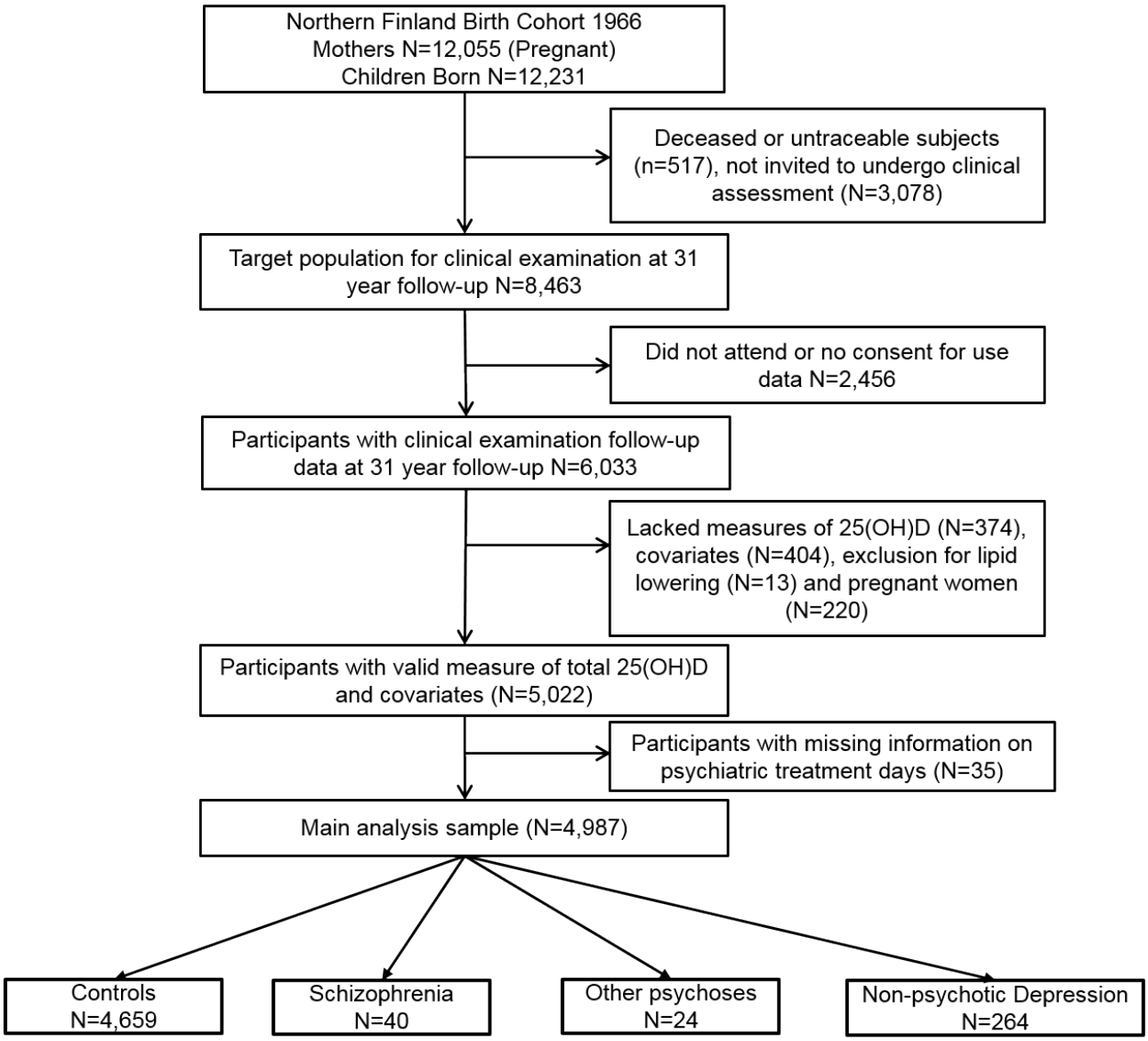

Figure 2. Vitamin D z–score in control, schizophrenia, other psychoses and non–psychotic depression individuals in NFBC1966

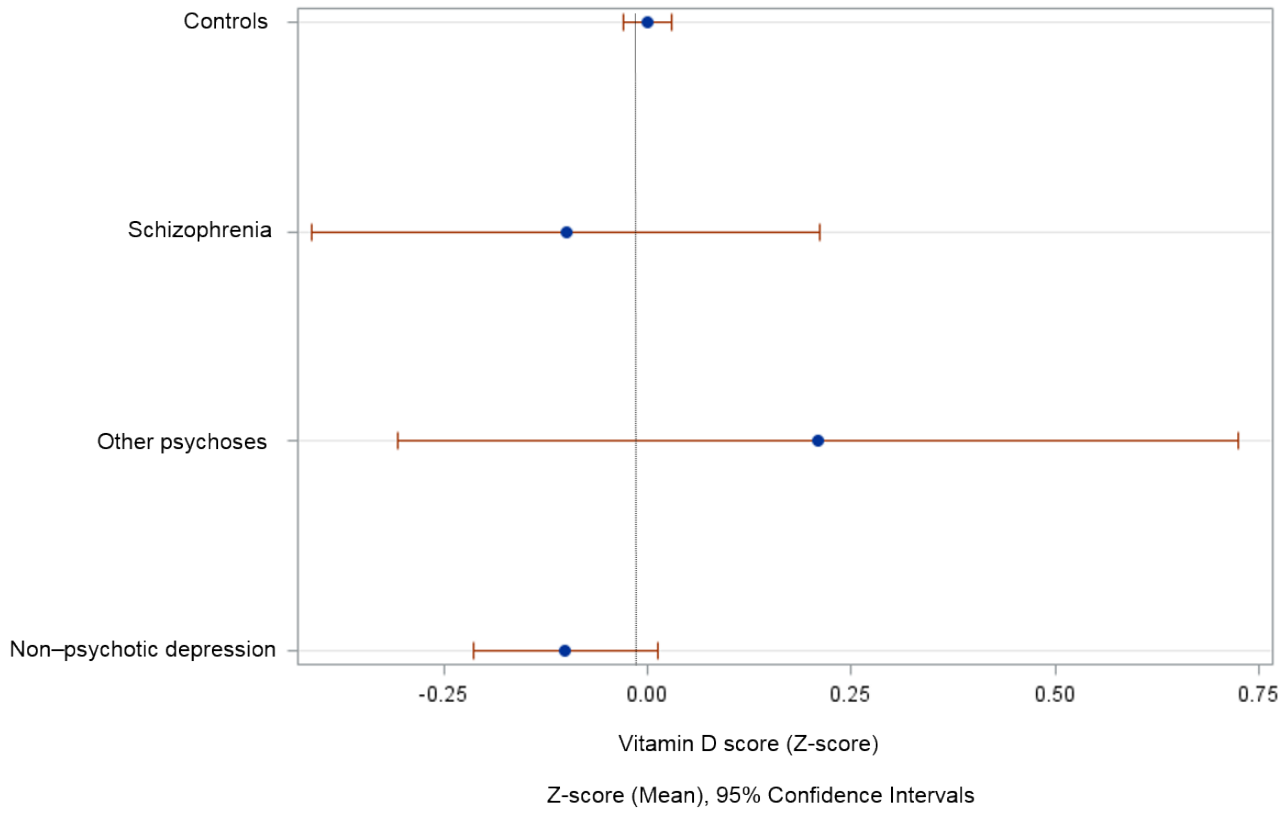

Table 1: Characteristics of the study groups in NFBC1966

Variables	Schizophrenia		Other psychoses		Non-psychotic depression		Control		*P*-value
	N=40		N=24		N=264		N=4,659		
	N or mean or median	% or 95% CI or range	N or mean or median	% or 95% CI or range	N or mean or median	% or 95% CI or range	N or mean or median	% or 95% CI or range	
Sex, N (%)									
Male	22	55	14	58	116	44	2315	50	
Female	18	45	10	42	148	56	2344	50	0.21
Daylight Season of blood sampling[1]**,** N (%)									
High vitamin D months	25	63	16	67	152	58	2902	62	0.46
Low vitamin D months	15	38	8	33	112	42	1757	38	
Location[2]**,** N (%)									
Oulu city	8	20	5	21	46	17	860	19	
Other Provinces of Oulu and Lapland	30	75	15	63	158	60	3081	66	0.032
Helsinki area	2	5.0	4	17	60	23	718	15	
Anthropometry									
Body mass index (kg/m^2) mean (95% CI)	26.2	24.8–27.7	26.1	24.1–28.0	25.2	24.6–25.8	24.6	24.5–24.7	0.004
P-value (difference from control *vs*. each group)	0.013		0.089		0.028		Reference		
Waist circumference (cm) mean (95% CI)	91.9	87.2–96.7	87.4	81.7–93.0	84.2	82.6–85.8	83.6	83.3– 83.9	<0.01
P-value (difference from control *vs*. each group)	<.0001		0.12		0.44		Reference		
Socioeconomic position, N (%)									
Professional & skilled worker	2	5.0	3	13	48	18	1148	25	0.001
Others	38	95	21	88	216	82	3511	75	
Lifestyle factors									
Smoking, N (%)									
Non-smoker	14	35	9	38	102	39	2082	45	0.20
Former/occasional smoker	8	20	7	29	74	28	1200	26	
Active smoker	18	45	8	33	88	33	1377	30	
Alcohol consumption (g/day), mean (95% CI)	5.4	2.2, 8.5	12.0	5.1, 18.9	13.0	9.9, 16.1	9.5	9.0, 10.0	0.14
Diet score (N/%)[3]									
Healthy	34	85	20	83	229	87	4131	89	0.44
Unhealthy	6	15	4	17	35	13	528	11	
Physical activity, Mean (95% CI)	14.0	7.9–20.0	10.6	5.9–15.3	14.4	12.6–16.2	14.9	14.5– 15.3	0.08
Oral contraceptive pills, N% of females[4]	4	22	1	10	39	27	576	25	0.94
Psychiatric treatment days, (median+range)	92.5	21.5-203.0	29.5	12.5-109.5	0.0	0.0	0.0	0,0	<0.01
Onset age (mean+95% CI)[5]	26.7	21.1–28.8	26.3	21.8–30.3	27.9	21.3–30.0	-		
Antipsychotic and antidepressant medication (N/%; N/%)[6]	13 / 0	41 / 0.0	4 / 2	27 / 7.4	1 / 17	0.5 / 9.2	5 / 9	0.4 / 0.7	<0.01

1. High vitamin D months [summer (1st of June - 30th of August), autumn (1st of September - 31st of October)] and low vitamin D months [winter (1st November - 31st of March) and spring (1st April - 31st of May)].
2. Latitudes: Oulu city 65º, Other Provinces of Oulu and Lapland ≥65º, Helsinki 60º.
3. An unhealthy diet included daily or frequent consumption of red meat and less frequent consumption of rye or crisp bread, berries or fruit, salads and vegetables.
4. Postal questionnaire data on contraception at 31 years had 42 missing female subjects. Percentages were counted from the number of subjects answered. The questionnaire was categorised in four groups: males, females with no contraception, females with contraception other than oral contraceptives and females with oral contraceptive pills.
5. There were 2 missing observations in schizophrenia and 1 missing observation in other psychoses group. Median and range are presented because of skewed distribution.

6. Questionnaire data of antipsychotic and antidepressant medication had 2,461 subjects missing. Percentages were counted from the number of subjects answered (N=2,526). Medications were classified to antipsychotics and antidepressants by ATC-coding. The remaining percentage is with no reported medication.

Table 2: Mean 25(OH)D concentration and vitamin D z-score in NFBC1966 participants

	Schizophrenia		Other psychoses		Non-psychotic Depression		Control		*P*-value
	N=40		N=24		N=264		N= 4,659		
	Mean	**(95% CI)**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	
Serum 25(OH)D concentration (nmol/L)	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[1]	-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

[1]The score was created by taking into account adjustment for season of blood sampling, latitude and 25(OH)D batch.

Table 3: Vitamin D status in NFBC1966 participants

Vitamin D status (IOM, 2010)	***n* (%)**
Deficiency (<30 nmol/L)	161 (3.2)
Insufficiency (30-50 nmol/L)	1,270 (25.5)
Sufficient (>50 nmol/L)	3,556 (71.3)

Table 4: Vitamin D status in schizophrenia, other psychoses, non–psychotic depression and control individuals (IOM, 2010)

Vitamin D status (IOM, 2010)	Schizophrenia	Other psychoses	Non–psychotic depression	Control
	N=40	N=24	N=264	N=4,659
Deficiency (<30 nmol/L)	1 (2.5)	0 (0.0)	11 (4.2)	149 (3.2)
Insufficiency (30-50 nmol/L)	11 (27.5)	7 (29.2)	80 (30.3)	1172 (25.2)
Sufficient (>50 nmol/L)	28 (70.0)	17 (70.8)	173 (65.5)	3338 (71.6)

Table 5: Correlation of vitamin D z-score with anthropometry, lifestyle, socioeconomic and psychiatric factors in NFBC1966

	Schizophrenia		Other psychoses		Non–psychotic Depression		Control	
	N=40		N=24		N=264		N=4,659	
	r	***p*-value**	***r***	***p*-value**	***r***	***p*-value**	***r***	***p*-value**
Anthropometry								
BMI[1]	0.082	0.62	-0.37	0.078	-0.037	0.55	-0.047	0.0015
WC[1]	0.0071	0.97	-0.29	0.17	-0.032	0.60	-0.063	<.0001
Lifestyle factors								
Physical activity[1]	-0.060	0.72	0.14	0.52	0.076	0.22	0.0065	<.0001
Diet [2]	-0.23	0.15	-0.24	0.25	-0.042	0.50	-0.029	0.045
Alcohol[1]	-0.25	0.13	0.16	0.45	-0.05	0.42	0.048	<.0001
Smoking[2]	-0.37	0.018	0.43	0.034	0.016	0.79	0.0064	0.66
SES[2]	0.040	0.81	-0.17	0.42	0.13	0.040	0.047	0.0015
Psychiatric treatment days[1]	-0.22	0.21	-0.014	0.95	-0.24	0.22	-	-

[1]Pearson correlation coefficients for normally distributed variables.

[2]Spearman correlation coefficients for categorical and skewed distribution.

Supplementary information

Supplementary Table 1: Vitamin D z–score in control, schizophrenia, other psychoses and non–psychotic depression individuals in NFBC1966

Variable*	*n*	Mean	SD	95% CI
Control	4659	-0.00	1.00	-0.03,0.03
Schizophrenia	40	-0.10	0.98	-0.41,0.21
Other Psychoses	24	0.21	1.22	-0.31,0.72
Non–psychotic depression	264	-0.10	0.93	-0.21,0.01

*The score was created by taking into account adjustment for season of blood sampling, latitude, 25(OH)D batch and sex.

Supplementary table 2: Serum 25(OH)D quintiles in NFBC1966 (*n*=4,987 subjects).

Quintile*	**Serum 25(OH)D mean (95% CI)**	***n* (%)**
Quintile 1	36.38 (36.0 - 36.8)	991
Quintile 2	50.79 (50.6 - 51.0)	1,007
Quintile 3	63.40 (63.2 - 63.6)	1,001
Quintile 4	78.78 (78.5 - 79.1)	985
Quintile 5	110.86 (109.4 - 112.3)	1,003

*Using cuts for the 20th, 40th, 60th and 80thpercentiles.

Supplementary table 3: Vitamin D quintiles in schizophrenia, other psychoses, non-psychotic depression and control group in NFBC1966

Quintile*	Schizophrenia	Other psychoses	Non-psychotic depression	Control
	n=264	*n*=40	*n* =24	*n* =4659
	n (%)	*n* (%)	*n* (%)	*n* (%)
Quintile 1	64 (24.3)	12 (30.0)	3 (12.5)	912 (19.6)
Quintile 2	48 (18.2)	6 (15.0)	6 (25.0)	947 (20.4)
Quintile 3	58 (21.9)	6 (15.0)	6 (25.0)	931 (19.9)
Quintile 4	47 (17.8)	9 (22.5)	3 (12.5)	926 (19.9)
Quintile 5	47 (17.8)	7 (17.5)	6 (25.0)	943 (20.2)
P*-value	0.51	0.72	0.28	

* *P*-values between controls *vs.* schizophrenia and controls *vs.* other psychoses were examined Fischer's exact test. *P*-values between controls *vs.* non-psychotic depression was examined using chi-squared test.

Supplementary Table 4: Serum 25(OH)D in the total population without adjustment for confounders (season of blood sampling, latitude, 25(OH)D batch and sex)

Variable*	Schizophrenia	Other psychoses	Non-psychotic Depression	Control	*p*-value
	***n*=47**	***n*=26**	***n*=279**	***n*=5,074**	
	Mean (95% CI)	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**	
Serum 25(OH)D concentration (nmol/L)	62.9 (55.3 – 70.5)	79.9 (64.3 – 95.5)	65.0 (61.9 –68.0)	68.1 (67.4 – 68.9)	0.03

*Exclusion criteria: Pregnant women and lipid lowering medication users.