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The association between physical activity, vitamin D and 10 years change in blood pressure in young to middle- aged adults. A prospective HUNT study

Pål Atle Fagerli

Master's Thesis

Department of Human Movement Science

Faculty of medicine, institute of neuroscience

Norwegian University of Science and Technology (NTNU)

Trondheim, Norway

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Aknowledgement

The Nord-Trøndelag Health Study (Helseundersøkelsen i Nord-Trøndelag (HUNT) is the result of collaboration between the HUNT Research Centre, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), the Norwegian Institute of Public Health, and Nord-Trøndelag

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Abstrakt

Introduksjon: Prospektive studier på fysisk aktivitet og vitamin D i relasjon med endring i blodtrykk er manglende. Hensikten med denne HUNT studien, var å undersøke assosiasjonen mellom fysisk aktivitet og vitamin D i relasjon med endringer i blodtrykk/hypertensjon. Vi undersøkte også den mulige modifiserende effekten fysisk aktivitet kunne ha på vitamin D-blodtrykk forholdet og ``vice- versa``. **Material og metode**: Studie populasjonen var fra HUNT studien. Fra et tilfeldig utvalg av 5723 subjekter med målt serum 25(OH)D nivåer, så ble 2949 men og kvinner 19-55år uten baseline hypertensjon eller bruk av blodtrykksmedisiner fulgt opp for 10 år. **Statistikk**: Lineær regresjon ble brukt for å undersøke assosiasjonen mellom fysisk aktivitet, serum 25(OH)D nivåer og en 10 års endring i blodtrykk. Logistisk regresjon var brukt for å undersøke forholdet mellom PA, vitamin D i forhold til risiko for fremtidig hypertensjon. **Resultat**: I løpet av 10 års oppfølgingsperiode, så var høy og moderat fysisk aktivitet assosiert med en henholdsvis -3.39 og -2.92 mmHg lavere endring i systolisk blodtrykk sammenligna med den inaktive gruppa. Det ble også observert en modifiserende effekt av serum 25(OH)D nivåer, men fysisk aktivitet var ikke assosiert med en redusert risiko for fremtidig hypertensjon. Ingen signifikant assosiasjon ble observert mellom serum 25(OH)D nivåer og endring i blodtrykk, eller en fremtidig risiko for hypertensjon. I tillegg ble det ikke funnet en modifiserende effekt av fysisk aktivitet. **Konklusjon**: Fysisk aktivitet er assosiert med en lavere endring i systolisk blodtrykk, men ikke hypertensjon. Våre data indikere en modifiserbar effekt av vitamin D serum 25(OH)D nivåer. Mer forskning er nødvendig i større populasjoner med lengre oppfølgingstid for å konkludere om serum 25(OH)D nivåer er assosiert med endringer i blodtrykk, eller fremtidig hypertensjon.

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Abstract

Introduction: Prospective studies on physical activity, vitamin D in relation to changes in blood pressure are lacking. This HUNT study aimed to investigate the association between physical activity and vitamin D levels in relation to changes in blood pressure/hypertension. We also aimed to investigate the potentially modifiable effect of PA on vitamin D- blood pressure relationship and vice- versa. **Material and methods:** The study population was taken from the HUNT study. From a random sample of 5723 subjects with measured serum 25(OH)D levels, 2949 men and women 19-55 years old without baseline hypertension or medications use were followed up for 10 years. **Statistics** Linear regression was used to investigate the association between PA, serum 25(OH)D levels and a 10 year change in BP. Logistic regression was used to investigate the relationship of PA, vitamin D with risk of future hypertension. **Results:** During 10 years follow- up, high and moderate PA was associated with a respectively -3.39 and -2.92 mmHg lower change in SBP, compared to the inactive group. A modifiable effect in the high serum 25(OH)D subgroup was observed, PA was not associated with a reduced risk of future hypertension. No significant association were observed between serum 25(OH)D levels and change in BP, or future risk of hypertension. No modifying effect of PA was seen. **Conclusion:** PA is associated with a lower increase in SBP, but not associated with a future risk for hypertension. Our data indicates there may be a modifiable effect of vitamin D serum 25(OH)D levels. Additionally more research in larger samples with longer follow- up, is necessary to conclude if serum 25(OH)D levels are associated with changes in BP or future risk of hypertension.

1.0 Introduction

1.1 Background

Physical inactivity, vitamin D insufficiency and high blood pressure are highly prevalent worldwide [1-3]. In Norway, only one of five is reported to be sufficiently active accordantly to the recommendations of 30 minutes of moderate intensity a day [4]. Furthermore, vitamin D deficiency is reported to be 40% in the HUNT study [5]. High blood pressure is one of the leading risk factor for death worldwide[6]. It is also a risk factor for cardiovascular disease (CVD), which is the number one cause of death in the world [7]. Subjects with elevated systolic blood pressure (SBP) >120mmHg or a diastolic blood pressure (DBP) >80mmHg are associated with having a higher risk for CVD [8]. A blood-pressure rise to hypertension, defined as SBP ≥140mmHg or DBP ≥90mmHg [9] is associated with a further increased risk of CVD including coronary heart disease, stroke, arrhythmias, heart failure, renal, disease, and vascular dementia [7]. Hypertensive subjects are also shown to have greater occurrence of other risk factors for CVD, such as obesity, glucose intolerance, insulin resistance, hypercholesterolemia, and reduced high-density lipoprotein cholesterol [10]. Both physical activity (PA) and sufficient vitamin D levels are reported to be beneficial for cardiovascular health [11, 12], and newer evidence suggest a connection to blood pressure (BP). The association between physical activity, vitamin D and blood pressure need more clarifications.

1.2 Physical activity and blood pressure

PA is defined as any bodily movement produced by the skeletal muscles that increases the energy expenditure [13]. While physically active lifestyle have been seen to be necessary to sustain and increase good health [14], sedentary lifestyle on the other hand have been seen to increase the risk of CVD, hypertension, certain cancers, congestive heart failure, obesity, stroke, osteoporosis and type 2 diabetes [15]. The possible biological mechanisms in which PA alters the BP are not completely understood, but changes in endothelia function, [16, 17] nerve system[18] and renin angiotensin- system (RAS)[19] is possible mechanisms. Some observational studies have found an association between PA and BP, but after adjustment for BMI and other risk factors the association seems to disappear [20-22] . Few prospective studies have investigated the association between PA and change in BP as main outcome, but an association between PA and lower risk for future hypertension are reported [23-25]. The prospective association between PA and changes in blood pressure is still limited.

1.3 Vitamin D and blood pressure

Vitamin D is a fat-soluble vitamin that has traditionally been seen as an important vitamin in maintaining a healthy musculoskeletal status [26]. Vitamin D intake can come from dietary sources or from ultraviolet B (UVB) irradiation from the sun [27], which is seen as the most important source in the majority of the population [28]. The irradiation stimulates the synthesis of cholecalciferol in the skin that undergo hydroxylation in both liver and kidneys to respectively change to 25 hydroxyvitamin D (25(OH)D) and the active form 1,25-dihydroxyvitamin D [27]. Vitamin D status is measured through circulating metabolites of 25(OH)D [29]. Cross-sectional studies suggest that 25 (OH)D levels and UVB exposure through the skin is associated with lower BP [30-32]. An increased distance from the equator have shown to be accompanied with higher BP [33] and lower ambient UVB radiation [34]. The evidence in which there is a connection between vitamin D and BP is however mixed in both interventional studies [35-38] and observational prospective studies [39-44]. An alteration in RAS has been reported in animal studies [45] and in human studies [46] and are proposed to be a connected to serum 25(OH)D levels. Both intervention studies and prospective studies on the vitamin D/BP association are still limited [47]

1.4 Physical activity and vitamin D

Physical activity in subjects has been associated with higher vitamin D levels [48]. This association is proposed to be from more sunlight exposure during PA, which was concluded in a study that found only an association between PA and serum 25(OH)D levels in the summer/fall, and not in the winter/spring [49]. However, Touvier et al. [50] found an association between PA and serum 25(OH)D after adjustment for sun exposure and outdoor activities. If there is an association between PA, vitamin D in relation to BP, the magnitude of the association could be different in PA subgroups and vitamin D subgroups. To our knowledge, no one have investigated PA and vitamin D as effect modifiers for each other in connection to BP. Therefore, the aim of this prospective HUNT study is first to investigate the association between physical activity and changes in blood pressure and risk of hypertension. Thereafter, the study aims to investigate the association between serum 25(OH)D levels and changes in blood pressure and risk of hypertension. Finally, we would investigate physical activity and Vitamin D as effect modifiers for each other.

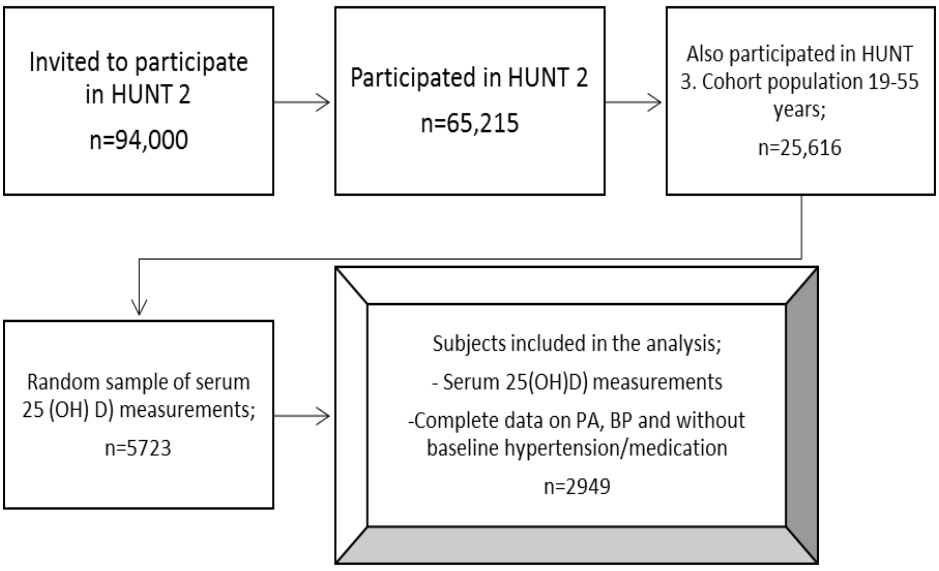
2.0 Materials and methods

2.1 Study Population

The participants were from the HUNT study (Helseundersøkelse I Nord-Trøndelag), which is a large population based health survey in Norway. The HUNT area is located in the middle of Norway represented primary by Caucasians (97%). Sociodemographic characteristics for the population is generally representative of Norway. Three surveys have been completed to date; (1984- 1986) HUNT1, (1995-1997) HUNT2 and (2006 – 2008) HUNT3 [51]. More information about HUNT can be found at http://www.hunt.no.

In HUNT2, 65,215 adults participated from an invited number of 94.000 adults, a response rate of 70%. Among these n= 37,059 (57%) also participated in HUNT3. We designed a cohort of the subjects that participated in both HUNT2 and HUNT3, and were 19-55 years old in HUNT2 n=25,616. From this cohort a random sample of n=5,723 subjects was selected to measure serum 25(OH)D levels from blood samples collected in HUNT 2. We then created a complete cohort with full information on PA, serum 25 (OH)D and BP measurement (n=4053). After excluding subject with baseline hypertension and BP lowering medication in HUNT2, 2949 subjects were left for the final analysis (Fig 1).We had baseline information on the three cohortsth to see if the population differed greatly. The study was approved by the Regional Committee for Ethics in Medical Research, and followed the Helsinki declaration.

Fig.1



2.2 Leisure-time physical activity

In HUNT2, the participants were asked about the intensity and duration of leisure-time PA during an average week in the last year. The intensity for light activity was defined as (no sweating/ not out of breath) while vigorous activity was defined as (sweating/out of breath). The response option for light and vigorous activity were 0, < 1, 1-2 and ≥3 hours per week. The participants were categorized into four PA groups based on the answers. Inactive. No light or vigorous PA. Low activity, 0-1 or 1-2 hours light and no hard PA. Moderate group as > 3 light and no vigorous PA or 0-1 hour vigorous PA with any light activity. High group as >1 hour vigorous activity with any light PA. This classification of PA is similar to other epidemiological studies conducted. [52, 53]

2.3 Serum 25 (OH)D

The serum 25(OH)D measurements were from blood samples collected in HUNT2. Random samples of n=5723 men and women were stored in freezers at -70 Celsius, and then further analysed using LIAISON 25- OH Vitamin D TOTAL (DiaSorin, Saluggia, Italy). The apparatus measured serum 25(OH)D levels using a fully automated antibody-based chemiluminescence assay, with an assay range of 10- 375 nmol/L. The coefficient of variation is 4% (intraassay), and coefficient of variation is 8% (interassay). Accuracy and precision of DiaSorin LIAISON 25-OH Vitamin D TOTAL has been validated as a consistent method to measure serum 25(OH)D levels [5].

Baseline measurements of 25(OH)D levels were categorized into three groups: <50nmol/L, 50-74,9nmol/L and >75nmol/l. These were created to define a ‘deficiency’, ‘insufficiency’ and ‘adequacy ‘vitamin D groups. These cut-off points are widely used in the literature [6].

2.4 Measurement of blood pressure

BP measurements were taken according to the protocol described in Holmen et al [54]. The subjects were sitting in a resting position with the arm on a table. A cuff was then placed around the upper arm to take measurements of BP and heart rate. BP was measured three times with a one- minute interval. A mean value based on the last two BP measurements was calculated to the nearest two mmHg for both SBP and DBP. The measurements were taken by trained health personnel with BP apparatus Dinamap Critikon model 845XT in HUNT2 and Dinamap Critikon model 8100 in HUNT3.

Changes in BP were calculated using the mean changes in mmHg from HUNT2 to HUNT3.

Hypertension was defined as SBP of ≥ 140mmHg or DBP ≥90mmHg or BP lowering medication.

2.5 Confounding factors

Data on variables was collected in HUNT 2. Potentially important confounders was included in the analysis as covariates, and categorized as age (19-29, 30-39, 40-49 or 50-55 years), sex (female/male), smoking (never, former, current, unknown), social benefits (none, any social benefits, unknown) economic difficulties in past year (no/yes, unknown) education (<10, 10-12, >13 years or unknown) alcohol consumption (Abstainer, or less than monthly, 1-4 times monthly, >=5times monthly, unknown), Family history of hypertension (FHHT) yes/no and BMI. Season of blood draw was categorized into four groups based on month of the blood sample: winter (12-2), spring (3-5), summer (6-8), autumn (9-11). This variable was only used in the adjustment, when vitamin D and BP was studied. The measurement of weight and height was done by trained personnel with the participants in light clothes with no shoes. Weight were measured to the nearest 0.5 kg and height to nearest 1.0 cm. Body mass index (BMI) was calculated with (kg/m^2), and categorized into four groups (normal <25, overweight 25-29,9 ,obese ≥ 30 or unknown).

2.6 Statistical analysis

The statistical analysis was conducted using STATA (Statistics/Data Analysis) version 13.1. For the descriptive statistics, the baseline characteristics were displayed using percentage distribution for the various variables with n=number for participants

The association between PA and 10-year change in SBP and DBP mmHg was investigated using linear regression in crude and adjusted analysis, with 95% confidence interval (CI). We first completed crude analysis, before we adjusted for covariates. In the adjusted analysis, all covariates were included without season of blood draw. To examine a potentially modifiable effect of serum 25(OH)D levels on the association between PA and BP, subgroup analysis was performed within the serum 25(OH)D <50nmol/L, and >50nmol/L groups. In the analysis, the inactive population was the reference group.

The same procedure was used to investigate the association between serum 25(OH)D and change in BP, but here the included season of blood draw was included as a confounder. In the subgroup analysis, we used (inactivity, light and moderate) as one group vs high PA to see a potentially modifiable effect. In the analysis, serum 25(OH)D <50 population was used as the reference group.

We also examined the association between levels of PA in association with future development of hypertension. Here we used logistic regression to calculated odds ratio (OR), and 95% CI in both crude and adjusted analysis. This was performed for the whole cohort and subgroups serum 25(OH)D > 50 and <50 group. This was done to investigate a potentially modifiable effect by serum 25(OH)D levels. All confounders except season of blood draw were included in the adjusted analysis, with the inactivity group used as reference. The OR was calculated for new cases of hypertension, over the approximately 10-year follow up.

We did the same analysis to investigate the association between serum 25(OH)D levels and development of hypertension. We investigated the association in the whole population and in subgroup PA (inactive, light, moderate) and high, to see a potentially modifiable effect by PA.

3.0 Results

Baseline characteristics for the final analysis-cohort n=2949 and the rest of the random vitamin D cohort n=5723 is shown in Table 1. The final analysis cohort showed a younger population with more reported PA. Data on other sociodemographic and lifestyle variables did not differ greatly.

The association between PA and 10 year changes in BP showed that higher levels of PA were associated with a lower increase in SBP mmHg (Table 2). The mean difference in change in SBP between the high PA group and the inactive group after adjustment was -3.39 (95% CI: -5.75 to -1.03). No significant association was observed for changes in DBP. In the subgroup analysis of serum 25(OH) D levels >50nmol/L, it showed a clear effect in SBP adjusted -4.45 (95% CI: -8.18 to -0.73) mmHg for the high PA compared to the inactive group. In the serum 25 (OH)D <50 nmol/L group no significant association was found between levels of PA and changes in SBP.

The association between serum 25(OH)D levels and 10 years change in BP showed no significant association with changes in SBP or DBP mmHg (Table 3). The adjusted mean difference in SBP between the serum 25(OH)D > 75nmol/L group compared to the <50 group was -0.50 (-2.00 to 1.00) mmHg. In the PA, high subgroup a possible tendency was found although there was no significant association. Serum 25 (OH)D >75nmol/L group compared to the reference 25 (OH)D <50 group had adjusted -1.65 (95% CI: -3.85 to 0.54) mmHg, lower change in SPB. No difference was observed for DBP.

We also investigated the continuous increase of 25 units of (OH)D and changes in BP. Here we used serum 25(OH)D as a continuous variable, and linear regression. A tertile regression was also conducted, to obtain a more comprehensive analysis of the relationship between serum 25(OH)D and BP. Both the continuous and tertile regression showed no significant association with change in BP (data not presented).

The 10- year association between levels of PA and the odds of development of systolic hypertension was investigated using logistic regression (Table 4). No association was found with adjusted OR 1.07 (95% CI: 0.65 to 1.76) for the high PA compared to the inactive reference group. No association was also seen in in the subgroup serum 25(OH)D >50 or <50 group, with respectively adjusted OR 0.94 (95% CI: 0.40 to 2.20) and 1.25 (95% CI: 0.66 to 2.34).

The 10- year association between serum 25(OH)D levels and the odds of development of systolic hypertension was investigated using logistic regression. No significant association was found between serum 25(OH)D levels and systolic hypertension, although a tendency in reduced OR were shown in the whole group and in the high activity subgroup (Table 5).

We defined hypertension in general including DBP≥ 90mmHg. However, because it showed similar results with defined hypertension of SBP≥ 140mmHg or medication use, we selected the last definition because of few reported cases of diastolic hypertension in HUNT3. We defined it also this way because we did not find an association between PA, vitamin D in relation to diastolic hypertension.

3.1 Baseline characteristics

Table 1. Baseline characteristics

2774 excluded

	Analysis cohort n. 2949		Sample with full information n. 4053		vitamin D cohort n.5723	
Age	n	%	n	%	n	%
19-29	602	20	717	18	888	16
30-39	1,053	36	1,303	32	1,736	30
40-49	1,005	34	1,509	37	2,227	39
50-55	289	10	524	13	872	15
Sex						
Female	1,705	58	2,102	52	3,135	55
Male	1,244	42	1.951	48	2,588	45
Smoking						
Never	1,276	43	1,739	43	2,365	41
Current	811	28	1,073	26	1,612	18
Former	690	23	1,014	25	1,422	25
Unknown	173	6	227	6	324	6
Physical activity						
None	133	5	200	5	236	4
Light	577	20	821	20	938	16
Moderate	1,043	35	1,421	35	1,622	29
High	1,196	41	1,611	40	1,835	32
Unknown					1,092	19
Social benefits						
None	1,897	64	2,652	65	3,643	64
Any social benefits	508	17	671	17	995	17
Unknown	544	18	730	18	1,085	19
Economic difficulties last year						
No	1,722	58	2,399	59	3,391	59
Yes	809	27	1,098	27	1,562	27
Unknown	418	14	556	14	820	14
Education						
<10	432	15	674	17	1,105	19
10-12 years	1,622	55	2,180	54	3,067	54
>13	881	30	1,179	29	1,496	26
Unknown	14	0	20	<1	55	1
Season of blood draw						
Winter (12-2)	835	28	1,204	30	1,739	31
Spring (3-5)	675	23	937	23	1,381	24
Summer(6-8)	374	13	464	11	697	12
Autumn(9-11)	1,065	36	1,447	36	1,904	33
Unknown						
Body mass index						
Normal	1,524	52	1,871	46	2,624	46
Overweight	1,175	40	1,732	42	2,414	42
Obese	241	8	440	11	673	12
Unknown	9	<1	10	<1	12	<1
Alcohol consumption						
Abstainer, or less than monthly	748	25	1,035	26	1,555	25
1-4 times monthly	1,732	59	2,329	57	3,204	59
>=5times monthly	406	14	599	15	782	14
Unknown	63	2	90	2	182	2
Family history of hypertension						
No	1,625	55	2,092	52	2948	52
Yes	1,324	45	1,961	48	2775	48
Vitamin D serum 25 (OH) D levels						
<50 nmol/L	1,426	48	2,059	50	3,001	52
>50-75 nmol/L	1,106	38	1,444	36	1,984	35
>75 nmol/L	417	14	550	14	738	13

Table 1. Baseline characteristics of vitamin D cohort n=5723 to the final analysis cohort n=2949.

3.2 Physical activity and change in blood pressure

Table 2. Linear regression for the 10-year association between PA and change in BP in whole group and in 25 (OH) D subgroups

SYSTOLIC				DIASTOLIC		
In analysis cohort N= 2949						
	Mean change in SBP mmHg.	Coeff. 95% CI Crude (a)	Coeff. 95% CI Adjusted (b)	Mean change in DBP mmHg.	Coeff. 95% CI Crude (a)	Coeff. 95% CI Adjusted (b))
Physical activity						
Inactive	4.68	0.00 (Reference)	Reference	-0.44	Reference	Reference
Light	3.38	-1.30 (-3.81 to -1.21)	-1.63 (-4.08 to 0.84)	-0.84	-0.40 (-2.06 to 1.27)	0.07 (-1.58 to 1.73)
Moderate	1.80	-2.87 (-5.28 to -0.47)	-2.92 (-5.29 to -0.56)	-1.53	-1.09 (-2.68 to 0.50)	-0.71 (-2.30 to 0.88)
High	0.82	-3.86 (-6.24 to -1.47)	-3.39 (-5.75 to -1.03)	-0.66	-0.22 (-1.80 to 1.36)	-0.10 (-1.69 to 1.48)
Population VitD <50 nmol/l (n= 1426)						
Physical activity						
Inactive	3.99	0.00 (Reference)	Reference	-1.24	Reference	Reference
Light	3.24	-0.75 (-3.97 to 2.47)	-0.91 (-4.10 to 2.28)	-1.30	-0.07 (-2.22 to 2.08)	0.43 (-1.72 to 1.58)
Moderate	0.92	-3.06 (6.18 to 0.04)	-2.93 (-6.03 to 0.17)	-1.75	-0.52 (-2.60 to 1.56)	-0.18 (-2.27 to 1.91)
High	1.41	-2.58 (-5.69 to 0.54)	-2.14 (-5.27 to 0.98)	-0.49	0.74 (-1.34 to 2.82)	0.77 (-1.33 to 2.88)
Population VitD >50 nmol/L(n = 1523)						
Physical activity						
Inactive	5.90	0.00 (Reference)	Reference	0.96	Reference	Reference
Light	3.58	-2.31 (-6.38 to 1.75)	-2.20 (-6.13 to 1.73)	-0.17	-1.13 (-3.80 to 1.54)	-0.30 (-2.95 to 2.36)
Moderate	2.63	-3.27 (-7.13 to 0.60)	-2.95 (-6.70 to 0.80)	-1.33	-2.28 (-4.82 to 0.25)	-1.62 (-4.15 to 0.91)
High	0.40	-5.50 (-9.32 to -1.66)	-4.45 (-8.18 to -0.73)	-0.78	-1.73 (-4.25 to 0.78)	-1.27 (-3.79 to 1.24)

a) Crude

b) Adjusted for age, sex, serum 25(OH)D, smoking, social benefits, economic difficulties, education, alcohol, FHHT, BMI

3.3 Vitamin D and change in blood pressure

Table 3. Linear regression for the 10-year association between serum 25(OH)D and change in BP in whole group and in PA subgroups

SYSTOLIC				DIASTOLIC		
In analysis cohort N= 2949						
	Mean change in SBP mmHg	Coeff. 95% CI Crude (a)	Coeff. 95% CI Adjusted (b)	Mean change in DBP mmHg	Coeff. 95% CI Crude(a)	Coeff.95% CI Adjusted (b)
Serum 25(OH)D)						
<50nmol/L	1.83	0.00 (Reference)	Reference	-1.18	Reference	Reference
50-74,9nmol/L	2.16	0.33 (-0.72 to 1.38)	0.06 (-1.02 to 1.14)	-0.93	0.25 (-0.45 to 0.94)	0.25 (-0.48 to 0.97)
>75nmol/L	1.06	-0.77 (-2.23 to 0.69)	-0.50 (-2.00 to 1.00)	-0.53	0.65 (-0.32 to 1.61)	0.54 (-0.46 to 1.55)
Physical activity (Inactive, Light, Moderate) N=1753						
Serum 25(OH)D)						
<50nmol/L	-0.45	0.00 (Reference)	Reference	-1.54	Reference	Reference
50-74,9nmol/L	1.06	1.52 (0.59 to 2.44)	0.54 (-0.87 to 1.95)	-1.04	0.50 (-0.41 to 1.41)	0.41 (-0.55 to 1.36)
>75nmol/L	-0.76	-0.31 (-1.62 to 1.00)	1.23 (-0.90 to 3.35)	-0.29	1.25 (-0.13 to 2.63)	1.00 (-0.44 to 2.43)
Physical activity (High) N=1196						
Serum 25(OH)D)						
<50nmol/L	1.41	0.00 (Reference)	Reference	-0.49	Reference	Reference
50-74,9nmol/L	0.94	-0.47 (-2.11 to 1.17)	-0.42 (-2.13 to 1.29)	-0.79	-0.30 (-1.38 to 0.78)	0.09 (-1.05 to 1.22)
>75nmol/L	-0.78	-2.19 (- 4.26 to -0.12)	-1.65 (-3.85 to 0.54)	-0.74	-0.25 (-1.61 to 1.12)	0.31 (-1.15 to 1.76)

a) Crude

b) Adjusted for age, sex, smoking, PA, social benefits, economic difficulties, education, alcohol, FHHT, Season of blood draw, BMI

3.4 Physical activity and hypertension

Table 4. Logistic regression for the 10 years association between PA and new cases of hypertension in whole group and in 25(OH)D subgroups.

	PA	Total	New cases (a)	Crude OR, 95 %CI	Adjusted
Physical activity	Inactive	133	25	1.00 (Reference)	(Reference)
	Low	577	121	1.15 (0.71 to 1.85)	1.29 (0.77 to 2.15)
	Moderate	1.043	181	0.91 (0.57 to 1.44	1.11 (0.68 to 1.83)
	High	1.196	191	0.82 (0.52 to 1.30)	1.07 (0.65 to 1.76)
Vitamin D >50	Inactive	48	8	1.00 (Reference)	(Reference)
	Low	237	53	1.4 (0.62 to 3.19)	1.71 (0.71 to 4.1)
	Moderate	539	94	1.03 (0.47 to 2.27)	1.14 (0.49 to 2.67)
	High	699	101	0.78 (0.35 to 1.71)	0.94 (0.40 to 2.20)
Vitamin D <50	Inactive	85	19	1.00 (Reference)	(Reference)
	Low	340	72	1.02 (0.56 to 1.84)	1.11 (0.59 to 2.11)
	Moderate	504	97	0.86 (0.48 to 1.53)	1.07 (0.57 to 1.99)
	High	497	106	0.97 (0.55 to 1.73)	1.25 (0.66 to 2.34)

Abbreviations: CI, confidence interval; OR, odds ratio

a New cases is defined as new cases of hypertension SBP >140 or use of medication. Multiadjusted: Age, sex, serum 25(OH)D, smoking, social benefits, economic difficulties, education, alcohol, FHHT, BMI

3.5 Vitamin D and hypertension

Table 5. Logistic regression for the 10 years association between baseline serum 25(OH)D and new cases of hypertension in whole group , and in PA subgroup

	Vitamin D (nmol/L)	Total	New Cases (a)	Crude OR, 95% CI	Adjusted
Total vitamin D	<50	1.426	272	1.00 (Reference)	(Reference)
	50- 74.9	1.106	195	0.91 (0.74 to 1.11)	0.98 (0.79 to 1.24)
	>75	417	51	0.59 (0.43 to 0.82)	0.73 (0.52 to 1.04)
PA High	<50	497	106	1.00 (Reference)	(Reference)
	50- 74.9	479	77	0.73 (0.52 to 1.02)	0.88 (0.59 to 1.30)
	>75	220	24	0.46 (0.28 to 0.75)	0.66 (0.38 to 1.15)
PA Low	<50	929	188	1.00 (Reference)	(Reference)
	50-74.9	672	125	1.05 (0.81 to 1.36)	1.08 (0.81 to 1.44)
	>75	197	30	0.74 (0.49 to 1.14)	0.90 (0.56 to 1.42)

Abbreviations: CI, confidence interval; OR, odds ratio

a New cases is defined as new cases of hypertension SBP >140 or use of medication. Multiadjusted: Age, sex, PA, smoking, social benefits, economic difficulties, education, alcohol, FHHT, Season of blood draw, BMI

4.0 Discussion

In this HUNT study we investigated the prospective association between PA, serum 25(OH)D levels and changes in blood pressure. In a cohort of 2949 subjects, men and women, 19-55 years old, high PA was associated with a lower change in SBP. This association was modified by the serum 25(OH) level. We found no association for DBP. For the association between serum 25(OH)D levels and changes in BP, no significant association was found for either SBP and DBP. PA did not modify this association significantly. The association between PA and hypertension showed no significant association, and no association was observed for serum 25(OH)D levels and hypertension. PA and serum 25(OH)D did not modify the association for each other.

4.1 Physical activity and blood pressure

An -3.39 CI: (-5.75 to -1.03) and -2.92 CI: (-5.29 to -0.56) lower change in SBP mmHg, was observed respectively in the PA high and moderate group compared to the inactive group in this study. This association was independent of BMI, age, sex and other covariates. This is similar to a longitudinal study, which found that PA were inversely associated with the development of hypertension [25], independent of BMI. In addition, two meta-analysis of random controlled trials (RCTs), found that training decreased SBP and DBP, in both pre-hypertensive and normotensive subjects [55, 56]. A possible explanation of a lower change in SBP observed in our study could be an improved endothelial function, which are reported in physically active subjects [16, 17]. An improvement in endothelia function may be due to increased release of nitric oxide (NO) during activity [57]. The vasodilation caused by NO could improve the vascular structure, reactivity and function [58] . Other explanations could be that PA influence the sympathetic nerve system, where the blood flow and neural control is altered, causing a reduction in systemic vascular resistance [18]. It is also possible that a lower activating of RAS due to PA could be associated to the findings in this study. Reduced BP with accompanied change in plasma- renin activity was seen in a study on endurance exercise on BP and other metabolic variables [19].

4.2 Vitamin D and blood pressure

No significant association was found between serum 25 (OH)D levels and changes in either SBP or DBP in this study. This is similar to results found in two prospective studies. In Margolis et al. [39] the association between serum 25(OH)D levels, blood pressure and

incident hypertension were investigated in postmenopausal women, where baseline serum 25(OH)D levels were not associated with the 7 years change in either SBP or DBP, and did not predict future hypertension. Jorde et al. [40] found an cross-sectional association between serum 25(OH)D levels and SBP, but not an prospective association between serum 25(OH)D levels and changes in SBP. A previous cross -sectional study that examined predicted vitamin D intake and blood pressure found an associated 6mmHg higher SBP in normotensive women 25-35 years who had an estimated vitamin D intake <400IU, compared to the estimated >400IU group. This association was found after adjustment for age, BMI , alcohol and calcium intake [41]. In the same study, the association was also found for normotensive older women 55 to 80 years, with 4mmHg higher SBP[41].

If vitamin D has any effect on lowering BP, it is suggested to be through the inhabitation of renin. Li et al. [45] demonstrated that a physiological levels 1.25(OH)2D) inhabited the expression of renin in the juxtaglomerular cells in the kidneys in mice. Furthermore, mice without vitamin D receptors had a 7 fold increased expression of renin. This is similar to a human study that found a higher circulating levels of angiotensin II in subjects with lower levels of 25(OH)D than subjects with 25(OH)D >75nmol/L [46]. This may again suggest that low 25(OH)D levels could lead to an upregulating of the renin-angiotensin system, and thereby higher BP.

4.3 Physical activity and hypertension

In our study, physically active subjects had an associated lower change in SBP than the inactive group, but not an accompanied reduced risk of hypertension. This is in contrast from a Finnish prospective study that found a reduced risk of hypertension (defined as new cases of hypertension treatment) in physically active 8302 men and 9139 women aged 25 to 64 years old, over a 11 years period [23]. The reason why they found a significant association may be that there was a high mean baseline SBP and DBP at respectively 139/84mmHg and 133/79mmHg for men and women. This means that the men was almost hypertensive according to the hypertension definition a SPB≥140 [9]. Hypertension at the defined levels, could lead to secondary alteration in the cardiovascular system [7]. It is also important to consider the possible residual confounding which could influence the finding from that study. A possible explanation of the lack of an association in our study could be that we had a relative young population with 56% under 40 years. Within 10 years follow-up, a change in blood pressure could occur, but without enough cases crossing the hypertension, level ≥

140mmHg and this may be the reason explaining why we did not find an association. In addition, a small number of subjects in the inactive group could possible influence our results towards null. However, a significantly small change in SBP in the PA high group compared to the inactive group, suggested that there may be a potential beneficial effect of PA on reducing future risk of systolic hypertension.

4.4 Vitamin D and hypertension

The lack of an significant association between serum 25(OH)D levels and hypertension is similar to another study. Forman et al, [42] investigated the vitamin D intake and risk of incident hypertension in three independent cohorts of a total 209.313 male and female participants [42]. The three cohorts found no association between vitamin D intake and risk of hypertension, even with very high estimated intakes of >1600 IU a day. However, in this study the vitamin D was predicted by food frequency questionnaire, even though sun exposure plays an important role in biosynthesis of vitamin D [59]. Another limitation in the study was that the blood pressure was not directly measured, but self-reported which could lead to bias in the data. In an intervention study, they found an effect of vitamin D supplementation on BP; however, this was in vitamin D deficient elderly women [35]. Two other studies found an association between measured serum 25(OH)D levels and incidence of hypertension; however these did not include measured BP, but self-reported hypertension [43, 44]

4.5 Public health implications

Observational data from 61 prospective studies, in men and women 40-89 years old showed that the risk of death from stroke and coronary heart diseases increased linearly from a SBP >115mmHg and DBP>75mmHg, in all age groups [60]. Our study supports the recommendations of 30 minutes moderate PA a day (similar to the high PA group in this study) could be beneficial for preventing an increase in SBP in young to middle-aged healthy adults. Preventing an increased systolic blood pressure above >120mmHg should be considered important. In a study conducted by Vatten et al. [61] an increased BP was associated with an increased risk of CVD death during a 16 years follow-up. The risk was also higher in men and women with no PA, compared to those that were physically active [61].

Although we did not find an association between PA and lower change in DBP in this study, the importance of lowering high SBP is large. High SBP is seen as a stronger predictor than high DBP for risk of cardiovascular events in middle-aged populations [8, 62]

4.6 Strengths

Our study has several strengths. Firstly, we had information about important confounders, such as BMI, smoking, alcohol, family history of hypertension, etc. We also had measured vitamin D levels, which is more objective measures of vitamin D, compared to predicted values. Additionally, we had also a long follow-up time of 10 years and BP measurement taken by trained personnel in both HUNT2 and HUNT3. Furthermore, new cases of hypertension were not self- reported, but defined by measurements in HUNT3 and new blood pressure medication use. We did not use self- reported hypertension, which could lead to misclassification. Lastly, this was one of the first study that investigated the interrelationship between PA, serum 25(OH)D and changes in BP in healthy young to middle-aged individuals.

4.7 Limitations

Our study has a number of limitations**.** As our study population was between 19 to 55 years old, the generalizability of our findings are limited to that age range. In addition because the population in the HUNT study is reported to be homogeneous consisting mainly of Caucasian, the result may not be representative of other ethnicities group. The questions about PA used in this study have been shown as a valid method to define the leisure time PA [63], however at the same time we cannot exclude that self-reported data, could lead to misclassification and incorrect categorization. If self-reported PA had influenced our results, it is likely that results were affected in a random order and not in a specific direction. Subjects with high amount of PA might exceed the options for the PA variable. Therefore, it is possible that subjects in PA high group could vary greatly in PA levels. When it comes to the association between vitamin D and blood pressure, we cannot rule out that an association could be found in a larger population, with longer follow-up period. In addition, only the marginal effect of vitamin D on BP should be considered important, considering that vitamin D deficiency is highly prevalent worldwide. Furthermore, we had only one measurement of vitamin D, and this could change over time resulting in misclassification of vitamin D levels. Lastly, we cannot rule out that possible residual confounding could be present even after adjustment for a panel of important confounders. In conclusion, the results of this 10 years prospective study in young to middle-aged Norwegian men and women showed that PA was associated with a

lower increase in SBP, but not associated with a future risk of hypertension. Our data indicates there may be a modifiable effect of vitamin D serum 25(OH)D levels. Additionally more research in larger samples with longer follow up, is necessary to conclude if serum 25(OH)D levels are associated with changes in BP or hypertension.

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