

Supplementary Online Content

Meyer HE, Willett WC, Fung TT, Holvik K, Feskanich D. Association of high intakes of vitamins B₆ and B₁₂ from food and supplements with risk of hip fracture among postmenopausal women in the Nurses' Health Study *JAMA Netw Open*. 2019;2(5):e193591. doi:10.1001/jamanetworkopen.2019.3591

eFigure. Flow of Inclusion for the Analyses of Vitamins B₆ and B₁₂ and Hip Fracture in the Nurse's Health Study Starting in 1984

eTable 1. Relative Risk (RR) of Hip Fracture According to Intake of Vitamin B₁₂ Among Women, the Nurses' Health Study (1986-2014)

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eTable 4. Relative Risk (RR) of Hip Fracture According to Intakes of Vitamins B₆ and B₁₂ Among Women, the Nurses' Health Study (1986-2014) (2,812 Hip Fractures), Current Intake

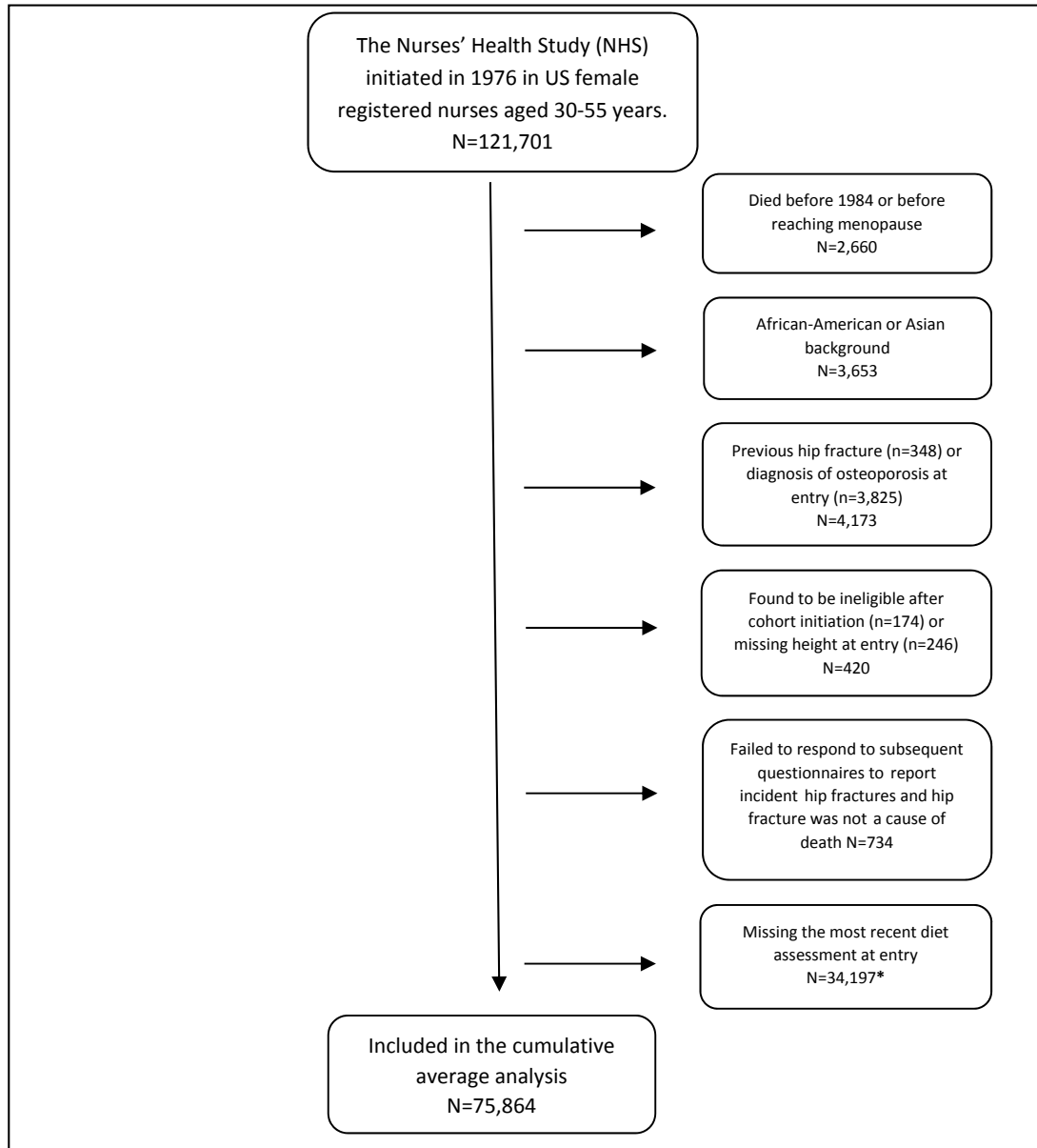
eTable 5. Relative Risk (RR) of Hip Fracture According to Current Intake of Vitamins B₆ and B₁₂ Among Women, the Nurses' Health Study (1986-2014) (2,812 Hip Fractures)

eTable 6. Randomized Controlled Trials Intervening With Both Vitamins B₆ and B₁₂ and Reporting on the Risk of Fracture

eReferences.

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Flow of inclusion for the analyses of vitamins B₆ and B₁₂ and hip fracture in the Nurse's Health Study, starting in 1984



* As dietary information at entry was a requirement for constructing cumulative average intakes, the sample size was lower for the **analysis using cumulative average intakes (n=75,864, with 2,304 hip fracture)** than for the **analysis using current intakes (n=96,467, with 2,812 hip fractures)** where this was not a prerequisite.

eTable 1. Relative risk (RR) of hip fracture according to intake of vitamin B₁₂ among women, the Nurses' Health Study (1984-2014). Cumulative average, stratified on physical activity.

Intake categories	Cases	RR (95% CI) (fully adjusted ^a)
Low physical activity (< median) (1528 hip fractures)		
Vitamin B₁₂ total (µg/day)		
< 5	119	1.00 (Ref)
5 –	478	0.88 (0.69-1.12)
10 –	579	0.93 (0.72-1.21)
20 –	157	1.14 (0.84-1.55)
≥ 30	195	1.06 (0.79-1.42)
<i>P value for linear trend</i>		0.021
High physical activity (≥ median) (723 hip fractures)		
Vitamin B₁₂ total (µg/day)		
< 5	40	1.00 (Ref)
5 –	196	1.34 (0.90-2.01)
10 –	289	1.45 (0.94-2.23)
20 –	66	1.33 (0.81-2.18)
≥ 30	132	1.65 (1.04-2.61)
<i>P value for linear trend</i>		0.51

^a Adjusted for age, questionnaire cycle, body mass index, height, physical activity, postmenopausal hormones, smoking status, cancer, cardiovascular disease, diabetes, osteoporosis, use of furosemide diuretics, thiazide diuretics, and oral steroids, and intakes of calcium, vitamin D, retinol, protein, caffeine, and alcohol.

eTable 2. Relative risk (RR) of hip fracture according to cumulative average intake of vitamins B₆ and B₁₂ among women, the Nurses' Health Study. Additional analyses adjusting for body mass index (BMI) four years previously and later weight change, self-reported health status, difficulties climbing a flight of stairs or walking one block, difficulty with balance, falls in the past year or pernicious anemia.

Intake categories	RR (95% CI) (‘fully’ adjusted ^a)	RR (95% CI) (additionally adjusted)
1988-2014 (2090 hip fractures)		
Vitamin B₆ total (mg/day)		<i>additionally adjusted for BMI 4 years ago and weight change^b</i>
< 2	1.00	1.00
2 –	1.11	1.12 (0.95-1.31)
5 –	1.18	1.19 (0.98-1.44)
15 –	1.12	1.12 (0.90-1.39)
≥ 35	1.32	1.31 (1.05-1.64)
<i>P value for linear trend</i>	<i>0.021</i>	<i>0.025</i>
Vitamin B₁₂ total (µg/day)		<i>additionally adjusted for BMI 4 years ago and weight change^b</i>
< 5	1.00	1.00
5 –	1.04	1.04 (0.83-1.29)
10 –	1.11	1.12 (0.88-1.41)
20 –	1.26	1.25 (0.96-1.64)
≥ 30	1.27	1.27 (0.99-1.64)
<i>P value for linear trend</i>	<i>0.039</i>	<i>0.04</i>
1992-2014 (2068 hip fractures)		
Vitamin B₆ total (mg/day)		<i>additionally adjusted for health status^c</i>
< 2	1.00	1.00
2 –	1.11	1.10 (0.94-1.30)
5 –	1.19	1.17 (0.96-1.43)
15 –	1.11	1.10 (0.89-1.37)
≥ 35	1.34	1.33 (1.06-1.67)
<i>P value for linear trend</i>	<i>0.013</i>	<i>0.013</i>
Vitamin B₁₂ total (µg/day)		<i>additionally adjusted for health status^c</i>
< 5	1.00	1.00
5 –	1.04	1.03 (0.82-1.28)
10 –	1.12	1.11 (0.87-1.41)
20 –	1.26	1.25 (0.95-1.64)
≥ 30	1.29	1.27 (0.98-1.64)
<i>P value for linear trend</i>	<i>0.013</i>	<i>0.019</i>
1992-2014 (2068 hip fractures)		
Vitamin B₆ total (mg/day)		<i>add. adj. for diff. climbing stairs, walking one block and balance^d</i>
< 2	1.00	1.00
2 –	1.11	1.11 (0.94-1.31)
5 –	1.19	1.18 (0.97-1.44)
15 –	1.11	1.10 (0.88-1.36)
≥ 35	1.34	1.33 (1.06-1.66)
<i>P value for linear trend</i>	<i>0.013</i>	<i>0.018</i>

Vitamin B₁₂ total (µg/day)		<i>add. adj. for diff. climbing stairs, walking one block and balance^d</i>
< 5	1.00	1.00
5 –	1.04	1.02 (0.81-1.27)
10 –	1.12	1.10 (0.86-1.40)
20 –	1.26	1.24 (0.94-1.62)
≥ 30	1.29	1.24 (0.96-1.60)
<i>P value for linear trend</i>	<i>0.013</i>	<i>0.03</i>

1998-2014 (1692 hip fractures)

Vitamin B₆ total (mg/day)		<i>additionally adjusted for falls^e</i>
< 2	1.00	1.00
2 –	0.98	0.98 (0.81-1.19)
5 –	1.03	1.03 (0.82-1.30)
15 –	0.99	0.98 (0.77-1.26)
≥ 35	1.19	1.18 (0.92-1.53)
<i>P value for linear trend</i>	<i>0.035</i>	<i>0.039</i>

Vitamin B₁₂ total (µg/day)

		<i>additionally adjusted for falls^e</i>
< 5	1.00	1.00
5 –	1.16	1.15 (0.87-1.52)
10 –	1.25	1.23 (0.92-1.65)
20 –	1.40	1.39 (1.01-1.91)
≥ 30	1.45	1.42 (1.05-1.93)
<i>P value for linear trend</i>	<i>0.009</i>	<i>0.015</i>

1998-2014 (1692 hip fractures)

Vitamin B₆ total (mg/day)		<i>additionally adjusted for pernicious anemia^f</i>
< 2	1.00	1.00
2 –	0.98	0.98 (0.81-1.19)
5 –	1.03	1.03 (0.82-1.30)
15 –	0.99	0.99 (0.78-1.26)
≥ 35	1.19	1.19 (0.92-1.53)
<i>P value for linear trend</i>	<i>0.035</i>	<i>0.035</i>

Vitamin B₁₂ total (µg/day)

		<i>additionally adjusted for pernicious anemia^f</i>
< 5	1.00	1.00
5 –	1.16	1.16 (0.88-1.53)
10 –	1.25	1.24 (0.93-1.67)
20 –	1.40	1.39 (1.01-1.92)
≥ 30	1.45	1.43 (1.05-1.94)
<i>P value for linear trend</i>	<i>0.009</i>	<i>0.020</i>

^a Adjusted for age, questionnaire cycle, BMI, height, physical activity, postmenopausal hormones, smoking status, cancer, cardiovascular disease, diabetes, osteoporosis, use of furosemide diuretics, thiazide diuretics, and oral steroids, and intakes of calcium, vitamin D, retinol, protein, caffeine, and alcohol

^b Control for BMI 4 yrs ago and weight change over the past 4 yrs.

^c Control for self-reported health status (agreement with "my health is excellent") - beginning in 1992

^d Control for difficulty climbing a flight of stairs or walking one block and difficulty with balance - beginning in 1992

^e Control for number of falls in the past year, beginning in 1998

^f Control for pernicious anemia, beginning in 1998

eTable 3. Relative risk (RR) of hip fracture according to cumulative average intake of vitamin B₆, vitamin B₁₂ and folate among women, the Nurses' Health Study (1984-2014) (2,304 hip fractures).

Intake categories	RR (95% CI) (fully adjusted ^a)	RR (95% CI) (additionally adjusted ^b)
Folate, total (µg/day)		
<i>adjusted for vitamin B₆</i>		
< 300	1.00	1.00
300 –	1.02	0.97 (0.82-1.15)
450 –	1.02	0.95 (0.78-1.16)
600 –	1.12	1.05 (0.84-1.30)
≥ 800	1.18	1.08 (0.84-1.40)
<i>P value for linear trend</i>	0.052	0.12
Vitamin B₆ total (mg/day)		
<i>adjusted for folate</i>		
< 2	1.00	1.00
2 –	1.11	1.13 (0.95-1.33)
5 –	1.17	1.18 (0.97-1.43)
15 –	1.10	1.11 (0.89-1.38)
≥ 35	1.29	1.29 (1.03-1.61)
<i>P value for linear trend</i>	0.059	0.14
Folate, total (µg/day)		
<i>adjusted for vitamin B₁₂</i>		
< 300	1.00	1.00
300 –	1.02	1.01 (0.87-1.18)
450 –	1.02	1.00 (0.83-1.20)
600 –	1.12	1.08 (0.88-1.32)
≥ 800	1.18	1.11 (0.87-1.42)
<i>P value for linear trend</i>	0.052	0.13
Vitamin B₁₂ total (µg/day)		
<i>adjusted for folate</i>		
< 5	1.00	1.00
5 –	1.01	1.02 (0.83-1.24)
10 –	1.09	1.08 (0.87-1.35)
20 –	1.21	1.20 (0.93-1.55)
≥ 30	1.25	1.22 (0.96-1.56)
<i>P value for linear trend</i>	0.017	0.044

^a Adjusted for age, questionnaire cycle, body mass index, height, physical activity, postmenopausal hormones, smoking status, cancer, cardiovascular disease, diabetes, osteoporosis, use of furosemide diuretics, thiazide diuretics, and oral steroids, and intakes of calcium, vitamin D, retinol, protein, caffeine, and alcohol

^b Folate additionally adjusted for vitamin B12 or vitamin B6. Vitamin B12 and B6 additionally adjusted for folate

eTable 4. Relative risk (RR) of hip fracture according to intake of vitamins B₆ and B₁₂ among women, the Nurses' Health Study (1984-2014) (2,812 hip fractures), current intake.

Intake categories	Cases	Crude incidence/10,000 ^a	RR (95% CI) (age and cycle adjusted)	RR (95% CI) (fully adjusted ^b)
Vitamin B₆ total (mg/day)				
< 2	490	12.1	1.00	1.00
2 –	1426	14.6	0.95 (0.86-1.06)	1.02 (0.90-1.15)
5 –	449	18.4	1.04 (0.91-1.19)	1.10 (0.94-1.29)
15 –	143	15.0	0.98 (0.81-1.18)	1.03 (0.84-1.27)
≥ 35	304	17.8	1.06 (0.92-1.23)	1.12 (0.95-1.33)
<i>P value for linear trend</i>			0.09	0.11
Vitamin B₆ suppl. (mg/day)				
0	733	11.4	1.00	1.00
< 2	589	14.8	1.14 (1.02-1.27)	1.23 (1.08-1.40)
2 –	927	18.1	1.14 (1.03-1.26)	1.24 (1.08-1.43)
5 –	150	15.1	1.27 (1.07-1.52)	1.37 (1.12-1.67)
≥ 25	413	17.3	1.19 (1.05-1.35)	1.29 (1.11-1.49)
<i>P value for linear trend</i>			0.17	0.18
Vitamin B₁₂ total (µg/day)				
< 5	314	12.8	1.00	1.00
5 –	737	11.8	0.95 (0.83-1.09)	1.04 (0.89-1.22)
10 –	803	14.4	1.05 (0.92-1.19)	1.13 (0.94-1.34)
20 –	312	16.9	1.00 (0.85-1.18)	1.10 (0.91-1.35)
≥ 30	646	22.7	1.15 (1.00-1.33)	1.26 (1.05-1.51)
<i>P value for linear trend</i>			<0.001	0.002
Vitamin B₁₂ suppl. (µg/day)				
0	502	13.6	1.00	1.00
<5	752	11.2	1.11 (0.99-1.25)	1.14 (1.00-1.29)
5 –	501	15.3	1.10 (0.97-1.24)	1.09 (0.93-1.28)
10 –	359	17.9	1.06 (0.93-1.22)	1.12 (0.96-1.32)
≥ 25	698	21.6	1.16 (1.03-1.31)	1.20 (1.04-1.39)
<i>P value for linear trend</i>			0.002	0.006

^a Per 10 000 person-years

^b Adjusted for age, questionnaire cycle, body mass index, height, physical activity, postmenopausal hormones, smoking status, cancer, cardiovascular disease, diabetes, osteoporosis, use of furosemide diuretics, thiazide diuretics, and oral steroids, and intakes of calcium, vitamin D, retinol, protein, caffeine, and alcohol

eTable 5. Relative risk (RR) of hip fracture according to combined current intakes of vitamins B₆ and B₁₂ among women, the Nurses' Health Study (1984-2014) (2,812 hip fractures)

Categories of total vitamin B ₆ and B ₁₂ intakes ^a	Cases	Person-years	RR (age and cycle adjusted)	RR (95% CI) (fully adjusted ^b)
Low B ₆ – Low B ₁₂	425	352622	1.00	1.00 (ref)
Med B ₆ – Low B ₁₂	601	492799	0.91	0.99 (0.86-1.14)
High B ₆ – Low B ₁₂	25	23103	0.90	0.97 (0.64-1.46)
Low B ₆ – Med B ₁₂	43	42242	1.16	1.07 (0.76-1.49)
Med B ₆ – Med B ₁₂	736	489055	1.02	1.09 (0.93-1.27)
High B ₆ – Med B ₁₂	24	12532	0.83	0.88 (0.57-1.35)
Low B ₆ – High B ₁₂	22	5277	1.09	0.99 (0.64-1.53)
Med B ₆ – High B ₁₂	681	167870	1.04	1.13 (0.96-1.33)
High B ₆ – High B ₁₂	255	122185	1.15	1.23 (1.02-1.49)

^a Cut-offs for vitamin B₆: 2 and 35 mg/day; Cut-offs for vitamin B₁₂: 10 and 20 µg/day

^b Adjusted for age, questionnaire cycle, body mass index, height, physical activity, postmenopausal hormones, smoking status, cancer, cardiovascular disease, diabetes, osteoporosis, use of furosemide diuretics, thiazide diuretics, and oral steroids, and intakes of calcium, vitamin D, retinol, protein, caffeine, and alcohol

eTable 6. Randomized controlled trials¹ intervening with both vitamin B₆ and B₁₂ and reporting on the risk of fracture.

Name of the trial (n)	Intervention	Fractures, n and type	Results, Relative risk (RR) for fracture	Comments
HOPE-2² (n=5522)	T ^a : 1mg vit B ₁₂ + 2.5mg folic acid + 50mg vit B ₆ C ^b : Placebo	N=313 (non-vertebral fractures)	RR=1.07 (0.85,1.33)	Number of hip fractures was not reported. HOPE2 also reported on vertebral fractures (n=50, RR= 0.93 (0.53-1.62) but they are less reliable as many are not clinically recognized.
VITATOPS³ (n=8164)	T: 0.5mg vit B ₁₂ + 2mg folic acid + 25mg vit B ₆ C: Placebo	N=145 (any fracture)	RR=0.86 (0.62,1.18)	A lower dose of vit B ₆ was used than the other trials. 70 hip fractures
WAFACS⁴ (n=4810)	T: 1mg vit B ₁₂ + 2.5mg folic acid + 50mg vit B ₆ C: placebo	N=349 (nonspine fractures)	RR=1.08 (0.88–1.34)	Increased risk in post hoc analysis of those with normal/high plasma vit B ₆ (RR 1.39 (1.01–1.91)) 22 hip fractures
NORVIT/WENBIT⁵ (n=6837) (factorial design)	T1: 0.4 mg vit B ₁₂ + 0.8mg folic acid + 40mg vit B ₆ T2: 0.4 mg vit B ₁₂ + 0.8mg folic acid T3: 40mg vit B ₆ C : placebo	N=236 (hip fractures)	T1 (B ₆ +B ₁₂ /folic acid) vrs. C: RR=1.49 (1.05-2.11) T2 (B ₁₂ /folic acid) vrs. C: RR of 0.89 (0.60-1.32) T3 (B ₆) vrs. C: RR of 1.19 (0.83-1.72)	Only hip fractures. The results are from an extended follow-up

^aT=treatment; ^bC=control;

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