骨への影響について追加を提案する論文、およびコメント（姫野）

ANSES 2017の結論とその根拠

Table 13: Chronic oral TRV based on bone effects

Critical effect	Critical dose	VTR
Osteoporosis or bone fractures Engström et al (2011 and 2012)	Urinary cadmium = 0.5 µg.g^{-1} of creatinine PBPK modeling	VTR = 0,35 µg Cd.kg pc^{-1}.j^{-1} Confidence level Medium

Table 10: Risks of osteoporosis and fractures following prolonged exposure to cadmium (CdU> 0.5 µg.g^{-1} creat) (Engström, 2011)

Urinary Cd		ORs (IC95%)	
		Σ Women	Non-smokers
Femoral neck			
	< 0,5 µg.g^{-1} créat.	1,00 (réf)	1,00 (réf)
	0,5-0,75 µg.g^{-1}créat	2,17 (1,51-3,11)	2,09 (1,12-3,93)
	>0,75 µg.g^{-1} créat	2,45 (1,51-3,97)	3,47 (1,46-8,23)
Lumbar spine			
	< 0,5 µg.g^{-1} créat.	1,00 (réf)	1,00 (réf)
	0,5-0,75 µg.g^{-1}créat	1,30 (0,91-1,86)	1,17 (0,64 -2,15)
	>0,75 µg.g^{-1} créat	1,97 (1,24-3,14)	3,26 (1,44-7,38)

Table 1. Characteristics of 2688 Women 56 to 69 Years of Age

	U-Cd, <0.50 μg/g of cr 0.30 (0.14–0.47)[a] $n = 2067$	U-Cd, 0.50–0.75 μg/g of cr 0.59 (0.51–0.72) $n = 449$	U-Cd, ≥0.75 μg/g of cr 0.87 (0.76–1.5) $n = 172$
Population characteristics[a]			
Age (years)	63 (60–69)	64 (60–69)	63 (60–69)
Education >9 years (%)	55	54	56
Total fat mass (kg)	26 (14–42)	26 (14–42)	25 (12–39)
Lean body mass (kg)	39 (33–47)	40 (33–47)	38 (32–45)
Parity (no. of children)	2 (0–4)	2 (0–4)	2 (0–4)
Ever use of postmenopausal hormones (%)	75	70	77
Ever use of oral corticosteroids (%)	5.9	6.0	5.8
Total physical activity (MET-hours/day)	41 (35–48)	41 (34–49)	41 (33–49)
Smoking: never/ever (%)	53/47	26/74	19/81
Alcohol consumption (g ethanol/day)	5.9 (0–21)	5.0 (0–22)	5.7 (0–20)
Biomarkers			
Urinary calcium (mg/g of cr)	146 (47–333)	161 (53–354)	157 (50–418)
Urinary magnesium (mg/g of cr)	96 (48–166)	98 (46–173)	96 (42–193)
Bone mineral density			
Total body (g/cm^2)	1.1 (0.97–1.3)	1.1 (0.95–1.3)	1.1 (0.92–1.2)
Femoral neck (g/cm^2)	0.89 (0.73–1.1)	0.88 (0.69–1.1)	0.85 (0.67–1.1)
Total hip (g/cm^2)	0.94 (0.75–1.2)	0.92 (0.72–1.1)	0.88 (0.68–1.1)
Lumbar spine (g/cm^2)	1.1 (0.86–1.5)	1.1 (0.85–1.4)	1.1 (0.77–1.5)
Volumetric femoral neck (g/cm^3)	0.35 (0.28–0.44)	0.34 (0.27–0.44)	0.33 (0.24–0.45)
Osteoporosis (T-score < –2.5)			
Femoral neck (%)	6.5	13	17
Total hip (%)	1.6	2.7	5.9
Lumbar spine (%)	9.1	11	17
Hip or spine (%)	13	19	24

[a]Median (5th to 95th percentiles) or percent.

Qing et al., Ecotox Env Safety 2021

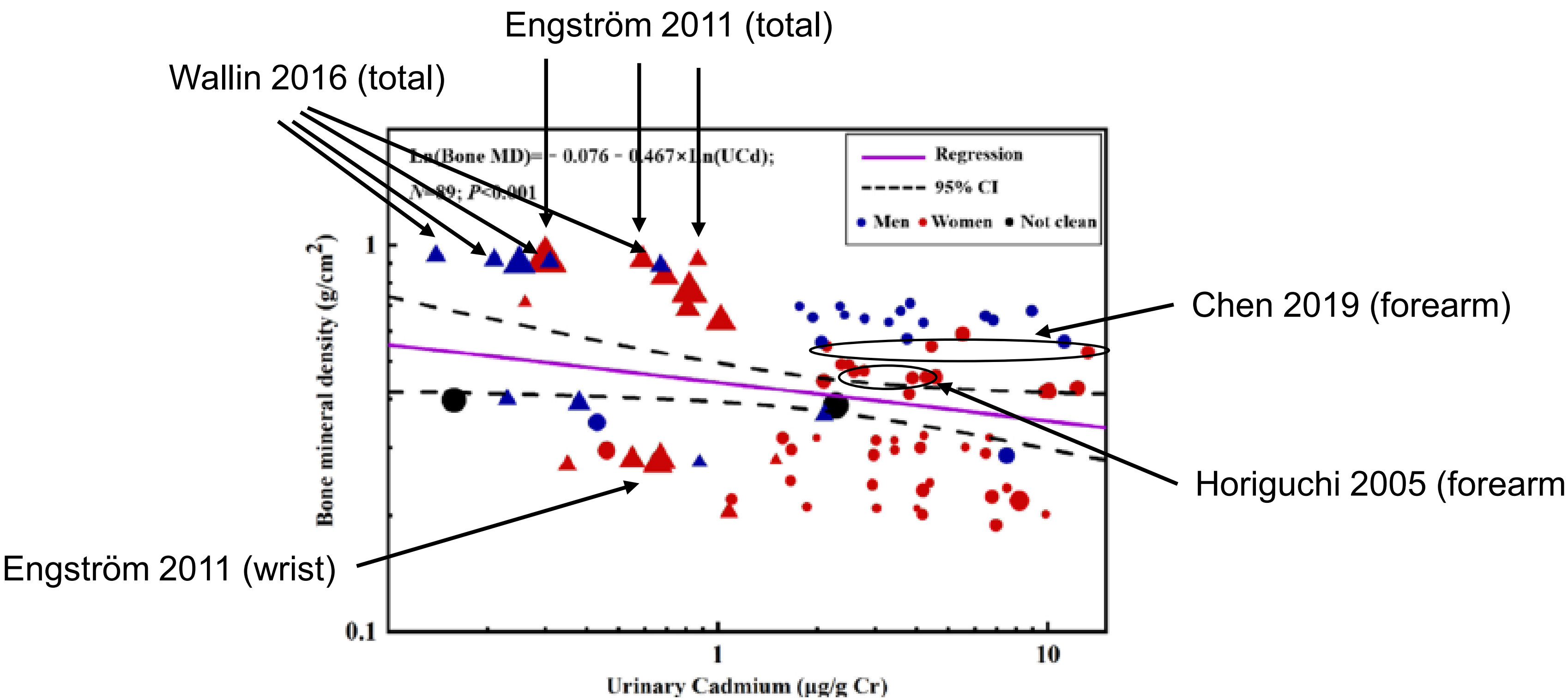


Fig. 2. The scatter plot of U-Cd and BMD (Color distinguishes gender (blue: men; red: women; black: gender information is no clear), shape represents ethnicity (triangle: Caucasian; circle: Asian); scattered point size represents the sample size of the data (Size = sqrt (sample size)/number of included studies)). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

この図は、骨密度の値に性差があるだけでなく、測定部位によって大きく異なること（全身＞前腕＞手首）を示している。同じ測定部位での骨密度を比較すると、尿中Cd濃度による低下傾向は極めてわずかである。

Horiguchi et al., Env Res 2005（第2版、今回のリストになし）

Table 3
BMD and BMI in subgroups divided by urinary Cd levels and age classes

Age classes	Urinary Cd (μg/g cr.)					Regression coefficients
	<2.5	⩾2.5, <3.5	⩾3.5, <5.0	⩾5.0	Total	
BMD (g/cm^2)						
All subjects	0.449 (0.078)	0.430 (0.077)*	0.412 (0.083)*	0.392 (0.086)*	0.421 (0.084)	−0.011**
	(range 0.185–0.623)	(0.213–0.624)	(0.210–0.644)	(0.219–0.680)	(0.185–0.680)	
Premenopause (41–48 y.o.)	0.489 (0.051)	0.484 (0.051)	0.495 (0.050)	0.490 (0.052)	0.489 (0.051)	0.001
Perimenopause (49–55 y.o.)	0.466 (0.064)	0.455 (0.063)	0.470 (0.065)	0.460 (0.075)	0.463 (0.066)	0.000
Younger postmenopause (56–65 y.o.)	0.407 (0.078)	0.399 (0.072)	0.388 (0.063)	0.378 (0.070)*	0.390 (0.070)	−0.006**
Older postmenopause (66–75 y.o.)	0.362 (0.073)	0.359 (0.069)	0.349 (0.068)	0.332 (0.062)*	0.346 (0.067)	−0.006**
BMI						
All subjects	23.9 (3.5)	23.7 (3.0)	23.7 (3.3)	23.6 (3.2)	23.7 (3.3)	−0.042
	(range 16.8–34.9)	(17.3–32.8)	(15.7–41.5)	(15.7–36.7)	(15.7–41.5)	
Premenopause (41–48 y.o.)	23.7 (3.3)	23.1 (3.1)	22.6 (3.0)	23.5 (3.1)	23.3 (3.2)	−0.033
Perimenopause (49–55 y.o.)	23.6 (3.3)	23.1 (3.0)	23.8 (4.1)	24.0 (3.1)	23.6 (3.4)	0.114
Younger postmenopause (56–65 y.o.)	24.5 (3.5)	24.3 (2.8)	23.8 (3.1)	23.5 (3.2)	23.9 (3.2)	−0.205**
Older postmenopause (66–75 y.o.)	25.1 (3.1)	24.7 (3.1)	24.1 (2.9)	23.6 (3.3)	24.2 (3.2)	−0.289**

Note: The values are presented as arithmetic mean (arithmetic standard deviation).
*Significantly different from the value in the lowest urinary Cd group (<2.5 μg/g cr.) judged by multiple comparison ($P<0.05$).
**Significant single regression coefficient ($P<0.05$).

BMDの測定部位は前腕。閉経前後の女性の年齢群別に解析。

Table 2 Stratification of subjects from the control and cadmium-polluted areas by age and menstrual status, and between-group comparison of body cadmium accumulation

	Control area	Cd-polluted area
Number of subjects		
All ages	123	129
<39 years	3	0
Premenopause (39–48 years)	22	27
Perimenopause (49–55 years)	43	32
Younger postmenopause (56–63 years)	36	41
Older postmenopause (64–69 years)	16	29
>69 years	3	0
Urinary Cd, μg/g cr., GM (GSD)		
All ages	3.36 (1.86)	6.30 (1.98)*
(Range)	(0.33–13.22)	(ND–23.67)
Premenopause (39–48 years)	1.99 (2.07)	3.42 (2.06)*
Perimenopause (49–55 years)	3.43 (1.88)†	5.61 (1.93)*†
Younger postmenopause (56–63 years)	4.39 (1.40)†	7.50 (1.68)*†
Older postmenopause (64–69 years)	4.01 (1.54)†	9.85 (1.46)*†
Regression coefficient	0.103	0.285**

Table 6 Comparison of bone mineral density and markers of bone metabolism between subjects in the control and cadmium-polluted areas

	Control area	Cd-polluted area
Bone mineral density, g/cm^2, AM ± ASD		
All ages	0.431 ± 0.078	0.423 ± 0.090
(Range)	(0.260–0.625)	(0.207–0.600)
Premenopause (39–48 years)	0.489 ± 0.048	0.484 ± 0.050
Perimenopause (49–55 years)	0.465 ± 0.059	0.471 ± 0.064
Younger postmenopause (56–63 years)	0.402 ± 0.070†	0.395 ± 0.083†
Older postmenopause (64–69 years)	0.358 ± 0.065†	0.354 ± 0.090†
Regression coefficient	−0.007**	−0.006**

Chen et al., J Exp Sci Env Epidemiol 2019（追加希望）

Table 1 Cadmium exposure levels, renal biomarker, and bone mineral density in men and women

Variables	Men ($n = 302$)				Women ($n = 488$)			
	Control ($n = 98$)	Moderately polluted ($n = 81$)	Heavily polluted ($n = 123$)	p value	Control ($n = 155$)	Moderately polluted ($n = 162$)	Heavily polluted ($n = 171$)	p value
Cd	0.48	2.14	11.00	<0.01	0.42	2.11	11.12	<0.01
Intake (g)	(0.27–0.65)	(1.77–2.33)	(9.72–11.61)		(0.26–0.62)	(1.76–2.33)	(9.63–11.62)	
UCd (μg/g cr)	2.06	3.74	11.23	<0.01	2.09	4.57	12.31	<0.01
	(0.44–4.52)	(0.19–7.53)	(2.68–27.32)		(0.30–5.66)	(1.43–14.02)	(3.54–45.63)	
BCd (μg/L)	1.37	3.98	9.34	<0.01	1.25	3.83	10.62	<0.01
	(0.50–4.96)	(1.24–11.23)	(2.41–26.67)		(0–3.42)	(0.88–11.51)	(3.07–37.68)	
UNAG (U/g cr)	2.53	5.04	8.08	<0.01	2.37	5.19	10.07	<0.01
	(0.02–5.63)	(0.11–25.07)	(0.60–60.0)		(0.12–13.2)	(0.20–31.8)	(2.0–46.4)	
BMD (g/cm^2)	0.76 ± 0.09	0.77 ± 0.08	0.76 ± 0.08	0.65	0.64 ± 0.11	0.65 ± 0.10	0.62 ± 0.11	0.15

Ucd cadmium in urine, *BCd* cadmium in blood, *UNAG* urinary N-acetyl-β-D-glucosaminidase, *BMD* bone mineral density

Cd intake, UCd, BCd, and UANG are shown as median (5–95% percentiles); BMD is shown as mean value ± standard deviation

BMD among the control and polluted areas was compared by using one-way ANNOVA. Others were compared by using the Kruskal–Wallis test

中国に、日本のイタイイタイ病発症地域に匹敵する高レベルのCd汚染地域が存在する。BMD（前腕部、SPA法）そのものはあまり低下していない。論文中では、女性で骨折が増加、さらに腎障害が強いほど骨折リスクが高くなることを記述。Cd intakeと尿中Cd、血中Cdが同じ集団で調べられている点も参考データとして重要。

Johnell et al., Osteoporos Int 1992

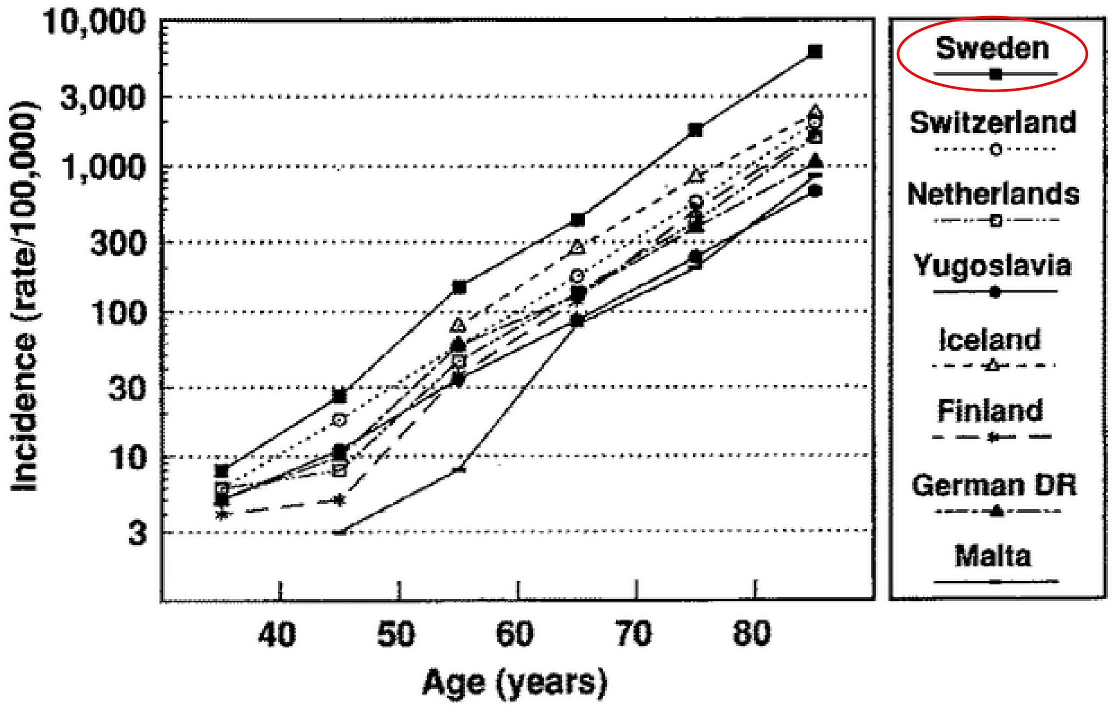
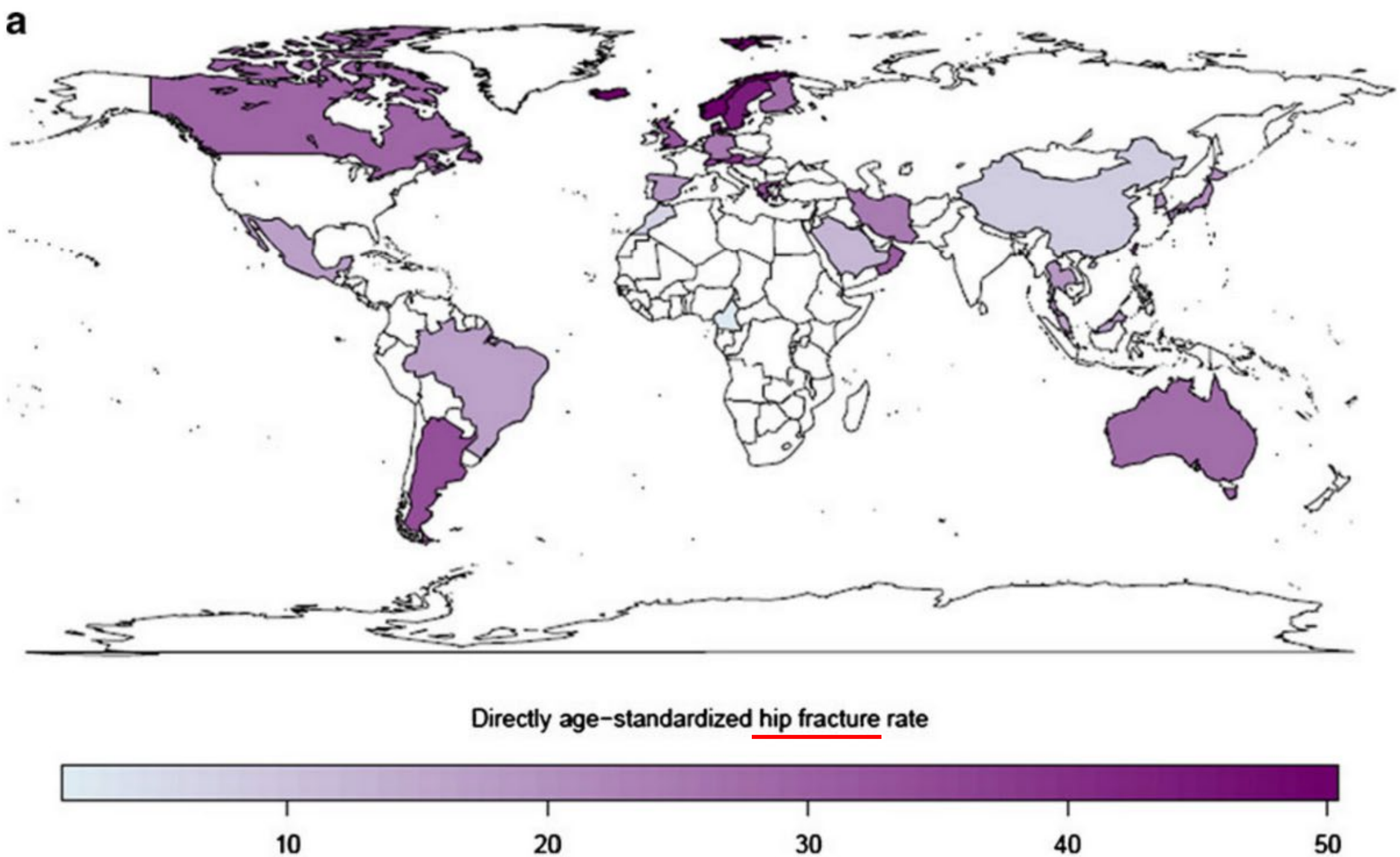


Fig. 1. Relationship of incidence of hip fracture to age in eight European countries. (German DR is the former GDR.)

欧州各国の年齢群別骨折発症率を比較すると、スウェーデンが最も高い。次に高いのはアイスランド。スウェーデンと他の欧州各国との差は3 - 10倍ある。年齢によって骨折リスクが顕著に増加することも明らか。論文中には具体的な数値あり。

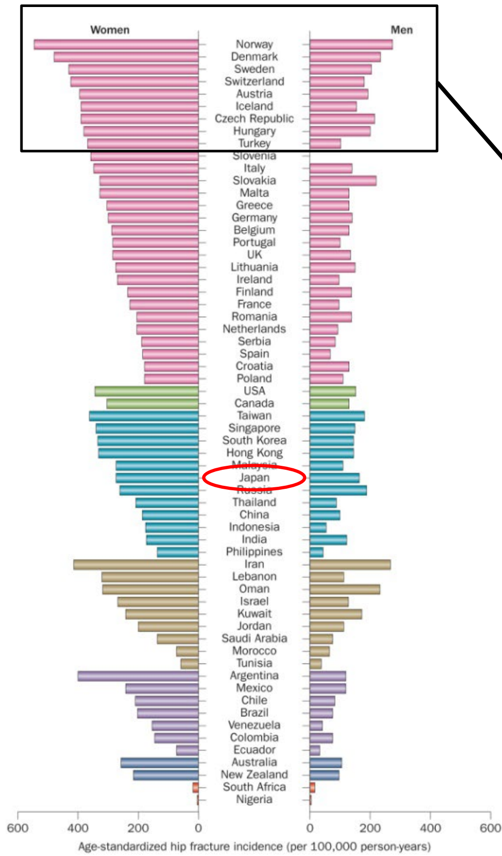
Cheng et al., Osteoporos Int 2011

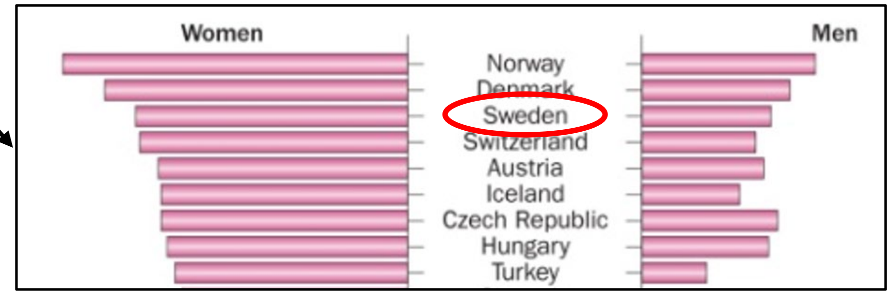
Women



世界各国の年齢調整後の骨折発症率の比較。スウェーデン、ノルウェー、アイスランドなどが最も高い。全体に、高緯度で、平均気温が低い国で、骨折発症率が高い。男性もほぼ同様。論文には具体的な数値あり。

Figure 1 Age-standardized hip fracture incidence rates in women and men according to country





2014年の論文においても、世界で最も骨折発症率が高いのは、ノルウェー、デンマーク、及び、スウェーデン。日本はアジアの中で中間的な位置にいる。

Cauley, J. A. *et al.* (2014) Geographic and ethnic disparities in osteoporotic fractures
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2014.51

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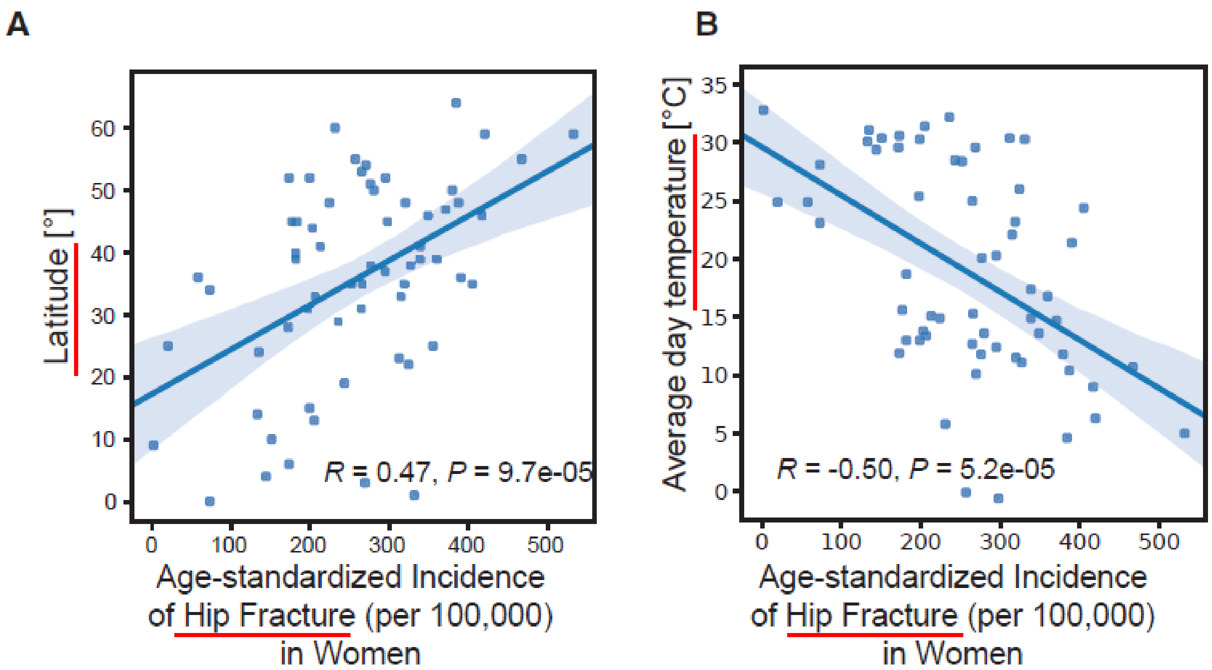

(A and B) Metadata analysis showing age-standardized correlation between hip fracture incidence (per 100,000 inhabitants) in women per country versus the latitude of the country's capitals (A) or versus the country's average day temperature (B).

Aは緯度が高い国ほど女性の年齢調整骨折発症率が高いこと、Bは平均気温が低いほど骨折発症率が高いことを示す。この論文は、環境温度が骨折発症に及ぼす影響を調べるため、マウスの腸内細菌に注目し、環境温度による腸内細菌の変化が原因である、とする動物実験の論文。上の図は、著者らの仮説を示すため、ヒトでの証拠として著者らが独自にまとめたもの。