

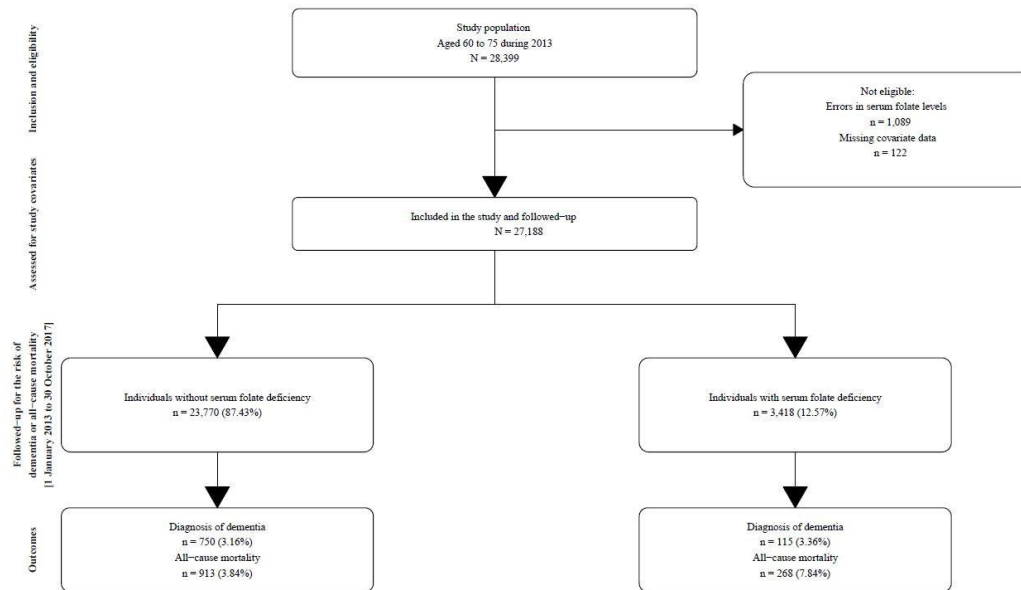
## **Serum Folate Deficiency and the Risks of Dementia and All-Cause Mortality:**

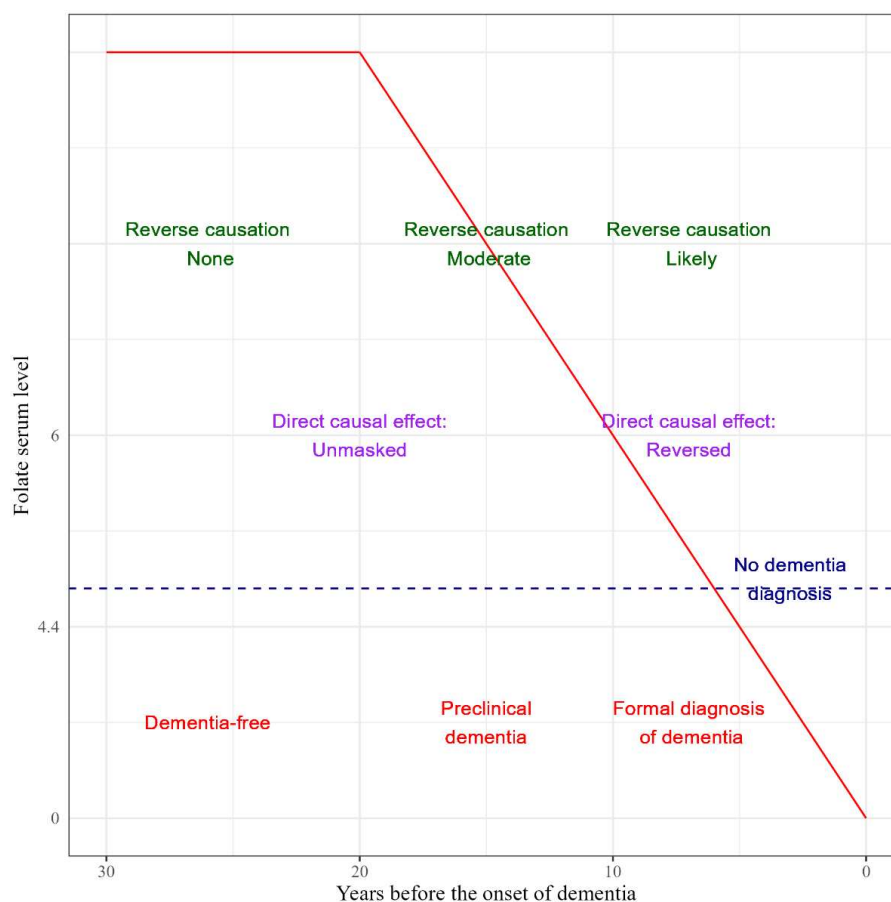
### **A National Study of Old Age**

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## Supplement Figure 1: Study flow diagram



**Supplement Figure 2: Illustration of the examination of reverse causation**

Note.

This figure was adapted from Kivimäki, et al.<sup>1</sup>

To examine reverse causation, the analysis was stratified by duration of follow-up. Based on the median follow-up cut point, the associations between serum folate deficiency and dementia or all-cause mortality were scrutinized in the first then second half of follow-up. Serum folate deficiency was assumed to be little affected by preclinical dementia when the assessment was long before dementia onset and considerably affected when the assessment was nearer the diagnosis. Therefore, a stronger association in the first half of follow-up time may suggest that reverse causation is likely.

1. Kivimäki M, Luukkonen R, Batty GD, et al. Body mass index and risk of dementia: analysis of individual-level data from 1.3 million individuals. *Alzheimer's & Dementia* 2018;14(5):601-09.

**Supplement Table 1: ICD codes for covariate diagnoses**

Health condition classification	ICD codes
Cognitive decline	ICD-9: 331.83, 780.93, 438.0, 294.9, 799.5x , ICD-10: G31.84, R41.81, R41.82, G31.9, F06.8, F06.7
Type II diabetes	ICD-9: 250.6, 250.5, 250.7, 250, 250.1, 250.4, 250.9, 362.01, 275, 250.2, 250.3, 648, 250.8, 251.3, 250.03, 250.02, 250.01, 366.41, 713.5, 362, 648.8, 250.61, 250.51, 337.1, 357.2, 790.29, 362.02, 362.29, 362.1  ICD-10: E11, E11.0X, E11.00, E11.01, E11.2X, E11.21, E11.22, E11.29, E11.3X, E11.31, E11.311, E11.319, E11.32, E11.321, E11.329, E11.33, E11.331, E11.339, E11.34, E11.341, E11.349, E11.36, E11.39, E11.4X, E11.40, E11.41, E11.42, E11.45, E11.49, E11.5X, E11.51, E11.52, E11.59, E11.6X, E11.61, E11.610, E11.618, E11.62, E11.620, E11.621, 11.622, E11.628, E11.63, E11.630, E11.638, E11.64, E11.641, E11.649, E11.65, E11.69, E11.8X, E11.9X
Depression	ICD-9: 296.1, 296.2, 296.22, 296.23, 296.24, 296.25, 296.26, 296.3, 296.31, 296.32, 296.33, 296.34, 296.35, 300.4,

**Supplement Table 2: The incidence of dementia and all-cause mortality per 10,000 person-years (95% confidence interval)**

Covariate	Classification	Dementia	All-cause mortality
Sex	Female	4.42 (3.24, 5.88)	4.76 (3.54, 6.27)
	Male	4.49 (3.17, 6.17)	7.91 (6.11, 10.05)
Smoking status	Non-smoker	4.44 (3.48, 5.58)	5.74 (4.64, 7.01)
	Smoker	4.48 (2.24, 8.01)	8.87 (5.55, 13.44)
Vitamin B12 deficiency	Absent	3.93 (0.09, 22.35)	4.93 (0.22, 24.08)
	Present <sup>1</sup>	4.46 (3.55, 5.52)	6.16 (5.09, 7.39)
Folic acid supplements	Absent	4.26 (3.32, 5.38)	5.38 (4.31, 6.62)
	Present <sup>1</sup>	5.64 (3.14, 9.35)	10.96 (7.32, 15.78)
Type II diabetes	Absent	3.82 (2.83, 5.04)	4.52 (3.44, 5.84)
	Present <sup>1</sup>	5.83 (4.05, 8.11)	9.68 (7.34, 12.51)
Depression	Absent	4.16 (3.27, 5.21)	6.09 (5.00, 7.34)
	Present <sup>1</sup>	10.34 (4.79, 19.49)	7.29 (2.81, 15.41)
Cognitive decline	Absent	2.62 (1.92, 3.50)	5.85 (4.78, 7.10)
	Present <sup>1</sup>	29.33 (20.76, 40.26)	10.10 (5.39, 17.24)
Serum folate deficiency	Absent	4.24 (3.34, 5.30)	5.36 (4.34, 6.54)
	Present <sup>1</sup>	7.96 (3.56, 15.32)	19.20 (11.84, 29.43)

Note.

<sup>1</sup>Presence at any time point during the follow-up.

**Supplement Table 3: Test of the proportional hazards assumption**

	Dementia		All-cause mortality	
	Chi-square	P-value	Chi-square	P-value
Birth year	0.04	0.84	0.004	0.95
Sex	0.36	0.55	0.0006	0.98
Smoking status	0.19	0.66	0.00001	0.99
Vitamin B12 deficiency	0.48	0.49	0.12	0.72
Folic acid supplements	0.02	0.89	0.22	0.64
Type II diabetes	0.54	0.46	0.35	0.56
Depression	0.56	0.45	0.09	0.77
Cognitive decline	1.24	0.27	0.96	0.33
Serum folate deficiency	0.82	0.37	0.01	0.90

Note.

All Chi-square values have DF = 1.

Non-significant values indicate that there was no significant departure from the proportional hazards assumption.

**Supplement Table 4: The primary analysis**

The competing Cox model of the associations between all study covariates and the risks of dementia and all-cause mortality

Covariate \ Outcome	Dementia			All-cause mortality		
	HR	95 % CI	P-Value	HR	95 % CI	P-Value
Birth year	0.86	(0.81, 0.91)	<0.001	0.88	(0.83, 0.92)	<0.001
Sex	0.92	(0.80, 1.06)	0.24	0.69	(0.61, 0.77)	<0.001
Smoking status	1.14	(0.93, 1.40)	0.21	1.38	(1.18, 1.61)	<0.001
Vitamin B12 deficiency	1.01	(0.55, 1.88)	0.96	1.44	(0.81, 2.55)	0.21
Folic acid supplements	0.92	(0.77, 1.12)	0.41	1.47	(1.28, 1.70)	<0.001
Type II diabetes	1.28	(1.11, 1.48)	<0.001	1.89	(1.68, 2.13)	<0.001
Depression	1.63	(1.29, 2.06)	<0.001	1.10	(0.85, 1.43)	0.47
Cognitive decline	9.65	(8.32, 11.18)	<0.001	1.53	(1.27, 1.85)	<0.001
Serum folate deficiency	1.68	(1.32, 2.13)	<0.001	2.98	(2.52, 3.52)	<0.001

Note.

Abbreviations: HR: Hazard Ratio from the Cox regression model, CI: Wald two-sided 95% confidence interval, P-Value: p-value for the test of the hypothesis HR=1 vs. the hypothesis HR≠1.

The HR quantifies the risk of a specific event (i.e., all-cause mortality or dementia) as a function of a study covariate (e.g., with vs. without serum folate deficiency). For example, this table shows that serum folate deficiency was associated with a 1.68-fold increased risk of dementia, and a 2.98-fold increased risk of all-cause mortality.

Sex reference group = Male; non-reference group = Female; Smoking status reference group = Non-smoker; non-reference group = Smoker; Vitamin B12 deficiency reference group = Absent; non-reference group = Present; Folic acid supplements reference group = Absent; non-reference group = Present; Type II diabetes reference group = Absent; non-reference group = Present; Depression reference group = Absent; non-reference group = Present; Cognitive decline reference group = Absent; non-reference group = Present; Serum folate deficiency reference group = Absent; non-reference group = Present.

**Supplement Table 5: Sensitivity analyses examining reverse causation**

Adjusted Cox models of the associations between serum folate deficiency and the risks of dementia and all-cause mortality stratified by duration of follow-up

Serum folate deficiency	Dementia		All-cause mortality	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Analyzed to median follow-up time	1.74 (1.36-2.21)	<0.001	3.24 (2.72-3.85)	<0.001
Analyzed after the median follow-up time	0.98 (0.46-2.09)	0.97	2.02 (1.29-3.17)	0.002

Note.

Abbreviations. HR: Hazard Ratio from the Cox regression model, CI: Wald two-sided 95% confidence interval, P-Value: p-value for the test of the hypothesis HR=1 vs the hypothesis HR≠1.

Serum folate deficiency reference group = Absent; non-reference group = Present.

Serum folate deficiency is assumed to be little affected by preclinical dementia when assessed long before dementia onset and considerably affected when assessed nearer the diagnosis. In other words, a stronger association in the first half of follow-up time may suggest that reverse causation is likely. In this case, evidence for reverse causation were moderate for dementia and mild for all-cause mortality.



**Supplement Table 6: Sensitivity analyses examining the effects of possible modifiers**

Adjusted Cox models of the associations between serum folate deficiency and the risks of dementia and all-cause mortality with added interaction terms

Variable tested in interaction with serum folate deficiency	Dementia		All-cause mortality	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Cognitive decline absent	2.97 (2.49-3.54)	<.001	2.24 (1.69-2.96)	<.001
Cognitive decline present <sup>1</sup>	3.06 (1.93-4.86)	<.001	1.11 (0.75-1.67)	0.60
Depression absent	3.02 (2.54-3.58)	<.001	1.82 (1.42-2.32)	<.001
Depression present <sup>1</sup>	2.47 (1.26-4.82)	<.008	0.87 (0.38-1.96)	0.73
Type II diabetes absent	2.79 (2.22-3.5)	<.001	1.93 (1.44-2.57)	<.001
Type II diabetes present <sup>1</sup>	3.19 (2.54-3.99)	<.001	1.32 (0.88-2.00)	0.18
Male sex	2.59 (2.11-3.2)	<.001	1.91 (1.42-2.58)	<.001
Female sex	3.73 (2.91-4.78)	<.001	1.42 (0.98-2.08)	0.07
Non smoker	3.27 (2.71-3.93)	<.001	1.48 (1.11-1.96)	0.007
Smoker	2.28 (1.65-3.15)	<.001	2.55 (1.63-3.98)	<.001
Folic acid supplements absent	3.97 (3.3-4.77)	<.001	1.91 (1.46-2.49)	<.001
Folic acid supplements present <sup>1</sup>	1.58 (1.17-2.14)	0.003	1.20 (0.74-1.94)	0.45
Vitamin B12 deficiency absent	2.69 (0.71-10.20)	0.14	5.74 (1.49-22.20)	0.01
Vitamin B12 deficiency present <sup>1</sup>	2.98 (2.52-3.52)	<.001	1.64 (1.29-2.08)	<.001

Note.

Abbreviations:

HR: Hazard Ratio from the Cox regression model, CI: Wald two-sided 95% confidence interval, P-Value: p-value for test of the hypothesis HR=1 vs the hypothesis HR≠1.

<sup>1</sup>Presence at any time point during the follow-up.