

## **ONLINE SUPPLEMENTARY MATERIAL**

Supplement to: Pre-eclampsia and risk of dementia later in life: nationwide cohort study

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Supplementary Table A. Hazard ratios for dementia subtypes, by history of preeclampsia and attained age, in a cohort of women with  $\geq 1$  live births or stillbirths in the period 1978 to 2015 in Denmark, additionally adjusted for cardiovascular disease, stroke, chronic kidney disease, diabetes, and hypertension

Supplementary Table B. Hazard ratios for dementia subtypes based on the last dementia diagnosis registered in the study period, by history of preeclampsia and attained age, in a cohort of women with  $\geq 1$  live births or stillbirths in the period 1978 to 2015 in Denmark

Supplementary Table C. Results of sensitivity analyses conducted to evaluate whether confounding by obesity ( $\text{BMI} \geq 30$ ) could explain the observed associations between a history of preeclampsia and overall dementia, vascular dementia, and Alzheimer's disease

References connected with Supplementary Table C

**Supplementary Table A. Hazard ratios for dementia subtypes, by history of preeclampsia and attained age, in a cohort of women with  $\geq 1$  live births or stillbirths in the period 1978 to 2015 in Denmark, additionally adjusted for cardiovascular disease, stroke, chronic kidney disease, diabetes, and hypertension**

Additional adjustment		Dementia overall		Vascular dementia		Alzheimer's disease		Other/unspecified dementia	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
<b>Overall</b>									
	None	1.53	1.26 to 1.85	3.46	1.97 to 6.10	1.45	1.05 to 1.99	1.40	1.08 to 1.83
	Cardiovascular disease	1.48	1.22 to 1.80	3.15	1.78 to 5.59	1.43	1.04 to 1.97	1.35	1.04 to 1.76
	Stroke	1.50	1.24 to 1.82	3.31	1.86 to 5.86	1.44	1.05 to 1.98	1.37	1.05 to 1.78
	Hypertension	1.36	1.12 to 1.65	2.34	1.32 to 4.15	1.42	1.03 to 1.96	1.22	0.93 to 1.59
	Diabetes	1.39	1.15 to 1.69	2.86	1.60 to 5.13	1.39	1.01 to 1.93	1.24	0.95 to 1.63
	Chronic kidney disease	1.52	1.25 to 1.84	3.55	2.01 to 6.26	1.42	1.03 to 1.96	1.40	1.07 to 1.82
	All comorbidities*	1.26	1.03 to 1.54	2.21	1.24 to 3.95	1.38	1.00 to 1.91	1.11	0.85 to 1.46
<b>Attained age</b>									
<b>&lt;65 years</b>									
	None	1.35	1.06 to 1.71	2.32	1.06 to 5.06	1.12	0.70 to 1.77	1.37	1.02 to 1.85
	Cardiovascular disease	1.30	1.03 to 1.65	2.21	1.01 to 4.84	1.10	0.69 to 1.74	1.34	1.00 to 1.80
	Stroke	1.31	1.03 to 1.66	2.12	0.97 to 4.64	1.11	0.70 to 1.76	1.35	1.00 to 1.81
	Hypertension	1.19	0.94 to 1.52	1.51	0.69 to 3.32	1.10	0.69 to 1.74	1.19	0.88 to 1.60
	Diabetes	1.25	0.98 to 1.58	2.01	0.91 to 4.43	1.07	0.67 to 1.69	1.28	0.95 to 1.72
	Chronic kidney disease	1.34	1.06 to 1.70	2.27	1.04 to 4.95	1.11	0.70 to 1.76	1.36	1.01 to 1.82
	All comorbidities	1.10	0.87 to 1.40	1.41	0.64 to 3.10	1.08	0.68 to 1.72	1.13	0.84 to 1.52
<b><math>\geq 65</math> years</b>									
	None	2.02	1.46 to 2.79	6.53	2.82 to 15.1	1.96	1.26 to 3.07	1.51	0.84 to 2.71
	Cardiovascular disease	1.96	1.42 to 2.71	5.91	2.55 to 13.7	1.92	1.23 to 3.00	1.43	0.79 to 2.56
	Stroke	1.99	1.44 to 2.76	5.88	2.54 to 13.6	1.95	1.25 to 3.05	1.44	0.80 to 2.58
	Hypertension	1.84	1.33 to 2.56	4.82	2.08 to 11.1	1.93	1.23 to 3.02	1.31	0.73 to 2.35
	Diabetes	1.80	1.30 to 2.50	5.03	2.11 to 12.0	1.85	1.18 to 2.91	1.27	0.70 to 2.29
	Chronic kidney disease	1.98	1.43 to 2.74	6.19	2.67 to 14.4	1.95	1.25 to 3.05	1.47	0.82 to 2.64
	All comorbidities	1.65	1.18 to 2.30	4.17	1.78 to 9.75	1.85	1.18 to 2.90	1.08	0.60 to 1.95

CI, confidence interval. HR, hazard ratio.

All hazard ratios for are adjusted for maternal birth year (5 to year intervals), parity (1, 2,  $\geq 3$  live births and/or stillbirths), and region of most recent delivery; age was the underlying time scale in the Cox model.

\* In sensitivity analyses in a sub to cohort excluding women using anti to hypertensive medication before 1995 or before their first birth, whichever came later (follow to up period: 1995 to 2015), the HRs overall vascular dementia, vascular dementia with onset <65 years, and vascular dementia with onset  $\geq 65$  years were HR 2.14, 95% CI 1.09 to 4.18, HR 1.31, 95% CI 0.52 to 3.31, and HR 4.45, 95% CI 1.68 to 11.8, respectively.

**Supplementary Table B. Hazard ratios for dementia subtypes based on the last dementia diagnosis registered in the study period, by history of preeclampsia and attained age, in a cohort of women with  $\geq 1$  live births or stillbirths in the period 1978 to 2015 in Denmark**

	History of preeclampsia	Person to years (x 10 <sup>3</sup> )	Vascular dementia			Alzheimer's disease			Other/unspecified dementia		
			No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI
<b>Overall</b>	Yes	972	11	2.45	1.31 to 4.57	47	1.60	1.19 to 2.15	55	1.38	1.05 to 1.81
	No	19380	99	1	Ref	679	1	Ref	837	1	Ref
<b>Attained age</b>											
<65 years	Yes	957	6	1.81	0.78 to 4.17	23	1.24	0.82 to 1.90	44	1.35	1.00 to 1.84
	No	18,999	70	1	Ref	417	1	Ref	665	1	Ref
$\geq 65$ years	Yes	15	5	4.08	1.57 to 10.6	24	2.19	1.44 to 3.33	11	1.46	0.79 to 2.69
	No	381	29	1	Ref	262	1	Ref	172	1	Ref
<b>Time since latest delivery</b>											
<20 years	Yes	779	3	2.67	0.79 to 8.95	4	0.86	0.31 to 2.33	18	1.20	0.74 to 1.93
	No	14,935	21	1	Ref	86	1	Ref	273	1	Ref
$\geq 20$ years	Yes	193	8	2.38	1.15 to 4.94	43	1.73	1.27 to 2.37	37	1.49	1.07 to 2.08
	No	4,445	78	1	Ref	593	1	Ref	564	1	Ref

CI, confidence interval. HR, hazard ratio.

Hazard ratios are adjusted for maternal birth year (5 to year intervals), parity (1, 2,  $\geq 3$  live births and/or stillbirths), and region of most recent delivery; age was the underlying time scale in the Cox model.

**Supplementary Table C. Results of sensitivity analyses conducted to evaluate whether confounding by obesity (BMI $\geq$ 30) could explain the observed associations between a history of preeclampsia and overall dementia, vascular dementia, and Alzheimer’s disease**

	Observed relative risk*	Prevalence of obesity among women with:		Relative risk for association between obesity and dementia	Adjusted relative risk†	95% CI	% bias‡
		No history of preeclampsia <sup>a</sup>	History of preeclampsia <sup>b</sup>				
<b>Overall dementia</b>	1.53	0.12	0.20	1.2	1.51	1.24 to 1.82	1.6
	1.53	0.12	0.25	1.2	1.49	1.23 to 1.80	2.5
	1.53	0.12	0.30	1.2	1.48	1.22 to 1.79	3.5
	1.53	0.12	0.20	1.5	1.47	1.21 to 1.78	3.8
	1.53	0.12	0.25	1.5	1.44	1.19 to 1.74	6.1
	1.53	0.12	0.30	1.5	1.41	1.16 to 1.71	8.5
	1.53	0.12	0.20	1.8	1.45	1.19 to 1.75	5.8
	1.53	0.12	0.25	1.8	1.40	1.15 to 1.69	9.5
	1.53	0.12	0.30	1.8	1.35	1.11 to 1.64	13.1
	1.53	0.12	0.20	2.1	1.42	1.17 to 1.72	7.8
	1.53	0.12	0.25	2.1	1.36	1.12 to 1.64	12.6
	1.53	0.12	0.30	2.1	1.30	1.07 to 1.57	17.5
<b>Vascular dementia</b>	3.46	0.12	0.20	2.0	3.23	1.84 to 7.14	7.1
	3.46	0.12	0.25	2.0	3.10	1.77 to 11.6	11.6
	3.46	0.12	0.30	2.0	2.98	1.70 to 16.1	16.1
	3.46	0.12	0.20	3.0	3.06	1.74 to 12.9	12.9
	3.46	0.12	0.25	3.0	2.86	1.63 to 21.0	21.0
	3.46	0.12	0.30	3.0	2.68	1.53 to 29.0	29.0
	3.46	0.12	0.20	4.0	2.94	1.67 to 17.7	17.7
	3.46	0.12	0.25	4.0	2.69	1.53 to 28.7	28.7
	3.46	0.12	0.30	4.0	2.48	1.41 to 39.7	39.7
	3.46	0.12	0.20	5.0	2.84	1.62 to 21.6	21.6
	3.46	0.12	0.25	5.0	2.56	1.46 to 35.1	35.1
	3.46	0.12	0.30	5.0	2.33	1.33 to 48.7	48.7
<b>Alzheimer’s disease</b>	1.45	0.12	0.20	1.5	1.40	1.01 to 1.92	3.8
	1.45	0.12	0.25	1.5	1.37	0.99 to 1.88	6.1
	1.45	0.12	0.30	1.5	1.34	0.97 to 1.83	8.5
	1.45	0.12	0.20	2.5	1.32	0.95 to 1.81	10.2
	1.45	0.12	0.25	2.5	1.24	0.90 to 1.71	16.5
	1.45	0.12	0.30	2.5	1.18	0.85 to 1.62	22.9
	1.45	0.12	0.20	3.5	1.26	0.91 to 1.72	15.4
	1.45	0.12	0.25	3.5	1.16	0.84 to 1.59	25.0
	1.45	0.12	0.30	3.5	1.08	0.78 to 1.48	34.6

\* Relative risk (in this instance, hazard ratios) estimated from the study data, without adjustment for obesity

† Relative risk for the association between history of preeclampsia and dementia, adjusted for obesity using the following

formula:  $RR_{adjusted} = \frac{ARR}{\frac{P_{c1}(RR_{cd}-1)+1}{P_{co}(RR_{cd}-1)+1}}$

‡ Calculated using the following formula:  $\% Bias = \left[ \frac{(ARR - RR_{adjusted})}{RR_{adjusted}} \right] * 100$

- a) We used available information from the Medical Birth Register on pre to pregnancy BMI (from 2004 onward) to estimate the prevalence of obesity ( $BMI \geq 30$ ) in women in our study population with no history of preeclampsia (the “unexposed” group).
- b) The prevalence of obesity in women in our study population with a history of preeclampsia was 23.3%, we evaluated potential confounding by obesity given prevalences in the “exposed” group of 20%, 25% and 30%. We also assessed the potential for confounding by obesity given a range of magnitudes for the association between BMI and dementia centered around estimates obtained from the literature (1–3).

## References

1. Albanese E, Launer LJ, Egger M, Prince MJ, Giannakopoulos P, Wolters FJ, et al. Body mass index in midlife and dementia: Systematic review and meta to regression analysis of 589,649 men and women followed in longitudinal studies. *Alzheimer's Dement Diagnosis, Assess Dis Monit.* 2017;8:165–178.
2. Anstey KJ, Cherbuin N, Budge M, Young J. Body mass index in midlife and late to life as a risk factor for dementia: A meta to analysis of prospective studies. *Obes Rev.* 2011;12(501).
3. Whitmer RA, Gunderson EP, Quesenberry CP, Zhou J, Yaffe K. Body mass index in midlife and risk of Alzheimer disease and vascular dementia. *Curr Alzheimer Res.* 2007;4(2):103–109.