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Prior placental bed disorders and later dementia: a retrospective Swedish register-based cohort study

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Objective To investigate the association between a history of placental bed disorders and later dementia.

Design Retrospective population-based cohort study.

Setting Sweden.

Sample All women giving birth in Sweden between 1973 and 1993 (1 128 709).

Methods Women with and without placental bed disorders (hypertensive disorders of pregnancy including pre-eclampsia, fetal growth restriction, spontaneous preterm labour and birth, preterm premature rupture of membranes, abruptio placenta, late miscarriages) and other pregnancy complications were identified by means of the Swedish Medical Birth Register. International classification of disease was used. Data were linked to other National Registers. Participants were followed up until 2013. The Cox proportional hazards model was used to calculate hazard ratios for women with and without pregnancy complications and were adjusted for possible confounders.

Main outcome measures Diagnosis of vascular dementia and non-vascular dementia.

Results Adjusted for cardiovascular disease and socio-demographic factors, an increased risk of vascular dementia was shown in women with previous pregnancy-induced hypertension (Hazard ratio [HR] 1.88, 95% CI 1.32–2.69), pre-eclampsia (HR 1.63, 95% CI 1.23–2.16), spontaneous preterm labour and birth (HR 1.65, 95% CI 1.12–2.42) or preterm premature rupture of membranes (HR 1.60, 95% CI 1.08–2.37). No statistically significant increased risk was seen for other pregnancy complications or non-vascular dementia even though many of the point estimates indicated increased risks.

Conclusions Women with placental bed disorders have a higher risk for vascular disease. Mechanisms behind the abnormal placentation remain elusive, although maternal constitutional factors, abnormal implantation as well as impaired angiogenesis have been suggested.

Keywords Alzheimer's disease, dementia, placental atherosis, placental disease, vascular dementia.

Tweetable abstract Placental bed syndromes associated with vascular dementia even after adjusting for cardiovascular disease.

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Introduction

Hypertensive disorders of pregnancy affect around 10% of women and several studies have shown that they are associated with later hypertension, ischaemic heart disease and stroke.[1–4] These disorders have also been linked to an increased risk of Alzheimer's disease.[5] Women with a historery of pre-eclampsia, hypertension in pregnancy with the addition of proteinuria, have a higher risk of cerebral white-matter lesions than women with normal pregnancies do.[6,7] These lesions are one of the signs of small vessel disease in the brain, which is associated with stroke and cognitive decline.[8] Also, these lesions have been shown to be independently associated with cognitive decline and are predictive of cognitive decline and dementia.[9] Further cognitive function has been shown to be affected in previous eclamptic and pre-eclamptic women several years after the index pregnancy.[10]

There are few studies testing the association between hypertensive disorders of pregnancy and Alzheimer's disease

and dementia. They have limitations, use different methods and have come to diverse conclusions,[11–14] but a recent large high-quality study showed an increased risk of vascular dementia, confirming a previous smaller study.[14,15]

Not only hypertensive disorders of pregnancy but also other obstetrical complications such as abruptio, certain forms of preterm birth and recurrent spontaneous abortions show a higher risk of cardiovascular disease in women in later life.[16]

Placental bed disorders (pre-eclampsia, intrauterine growth restriction, preterm labour and birth, preterm premature rupture of membranes, late spontaneous abortion and abruption placentae) have been linked with the development of abnormal placentation[17].

We found no studies examining the association between placental bed disorders and Alzheimer's disease and dementia.

The aim of this study was to investigate whether there is an association between a history of placental bed disorders and other pregnancy complications and later dementia in a national sample of women.

Methods

Study population

The study population was defined as women born prior to 1968, who gave birth between 1973 and 1993, and who had not died before reaching 20 years of age. No other limitations regarding inclusion in the study were applied. This resulted in a study population containing 1 128 709 women who were followed until 2013.

Registers included in the study

The data used in this study were based on the merger of information from several Swedish national population registers using the unique personal identification number assigned to every person residing in Sweden. Linking the information from the different registers was very straightforward, as both Statistics Sweden and the National Board of Health and Welfare had delivered information on all women born in Sweden between 1973 and 1993, where everyone had been given a unique code. The same unique code was used in all registers, e.g. code 1 identified the same person in each of the registers included in the study.

The following Registers were used: the Medical Birth Register (containing pregnancy and delivery-related information regarding mothers and newborn children),[18–20] the National Patient Register (containing information regarding specialised in- and outpatient care),[21–23] the Cause of Death Register (information on when the death occurred and the cause(s) of death),[24–27] the Multi-generation Register[28] to link children born between 1973 and 1993 and their parents, the Total Population Register[29] (to obtain information on marital status, country of birth and migrations), and the Education Register[30] and the 1970 Population and Housing Census[31] (to retrieve information regarding a person's level of education).

All these registers have been evaluated regarding content and quality. In-depth analyses of the registers' contents and quality were carried out by Cnattingius et al. in 1990, and in 2003 by the National Board of Health and Welfare themselves. In summary, the registers is covers 98–99% of all births in Sweden and is of good quality. The National Patient Register was evaluated in 2009 and is generally of good quality. However, there still remain some problems regarding coverage and quality on information from private caregivers and psychiatric diagnoses from outpatient clinics. In an evaluation of the quality of the Cause of Death Register, the conclusion was reached that the magnitude of coding errors ranged between 1 and 6%. The Multigeneration Register, the Education Register and the Total Population Register are all of very high quality. The Multigeneration Register has a nearly complete coverage of index persons born in 1961 and onwards, whereas the overall rate of missing data is 2.3% in the Education Register. The Total Population Register has reported a small over-coverage (i.e. inclusion of persons who have moved out of Sweden) of 0.2–3%.

Variables

Maternal educational level was separated into 'Elementary', 'High School', 'College/University' and 'Missing'. The category 'Missing' was kept as a separate level in the analyses as it mainly consisted of women with an immigrant background. Parity was defined as 'Primiparous' (having delivered only one child) or 'Multiparous' (having delivered more than one child). Infertility was coded as 'Yes' if the woman had ever reported prior infertility at any of her pregnancies, otherwise it was coded as 'No'. Maternal origin was divided into 'Nordic' and 'non-Nordic' place of birth. A variable indicating whether a woman had only given birth to girls or boys, or a combination of boys and girls was created.

Several variables indicating different aspects of possible placental bed disorders were used in the current study: pre-eclampsia, intrauterine growth restriction, preterm labour and birth, preterm premature rupture of membranes, late spontaneous abortion and abruption placentae as well as other placental anomalies (e.g. malformed placenta, adherent placenta, transfusion syndromes, infarctions), recurrent miscarriages, exaggerated intrauterine growth, gestational diabetes, intrauterine fetal death and infertility, each variable coded as 'Yes' or 'No', where 'Yes' indicates the presence of the disease at any of the pregnancies a woman may have had. Cardiovascular diseases were coded similarly, where a 'Yes' indicated that the woman had at any point been diagnosed with the specific

disease. Cardiovascular diseases included in the study were: heart failure, ischaemic heart disease, stroke, systemic lupus erythematosus (SLE), diabetes (excluding gestational diabetes) and hypertension.

The presence of dementia, pregnancy complications and cardiovascular disease was retrieved from the Swedish National Patient Register. ICD-10 codes were translated into equivalent codes for ICD-9 and ICD-8 to capture morbidity during the entire time period.

In the present study, the following diagnosws according to codes defined in ICD-10 were included: Dementia (F000–F009, F020, F023, F028, F030-F039, F051, G300–G309, G310, G311, G318), Vascular dementia (F010–F019), Alzheimer's disease (G300–G309), SLE (M329), Abruptio placentae (O450–0459), Pre-eclampsia (O119, O140-O149, O150–O159), Placental anomaly (O430–O439), Preterm labour and birth (O470, O471, O600, O601), Recurrent miscarriages (O262, N96), Fetal growth restriction (P050–P059), Intrauterine excessive growth (P080, P081), Infertility (N970, N978, N979), Intrauterine fetal death (O364, P950, P959), Preterm premature rupture of membranes (PPROM: O601), Hypertension (I109–I139, I150–I159), Pregnancy-induced hypertension (O139, O169), Ischaemic heart disease (I200-I259), Heart failure (I500–I509), Diabetes (E100–E119), Gestational diabetes (O244, O249), Stroke (I600–I698), Atherosclerosis (I700–I798).

To obtain a total measure of all types of dementia, a variable named 'any dementia' was created and included women having been diagnosed with vascular dementia, dementia and/or Alzheimer's disease.

No patient or patient organisation was involved in the planning or execution of the study.

Statistics

Bivariate analyses of types of dementia (any dementia, vascular dementia, dementia and Alzheimer) with respect to socio-demographic, placental/pregnancy diagnoses and cardiovascular disease were performed using Pearson's chi-square If the cell count was <5, Fisher's exact test was used instead of Pearson's chi-square. The likelihood of being diagnosed with different types of dementia (each type modelled separately) was estimated using Cox's proportional hazards model. Women entered the year they were born and exited the models the year they were diagnosed, the year they died or when they reached the end of the follow-up period. Unadjusted estimates were calculated for each of the socio-demographic and pregnancy factors as well as for cardiovascular disease (from the National Patient Register) included in the study as well as adjusted estimates where the hazard ratio for being diagnosed with dementia was adjusted for socio-demographic background variables and cardiovascular disease. Different models were evaluated, either only adjusting for socio-demographic variables or adjusting for both socio-demographic variables and cardiovascular disease.

All analyses were performed using IBM SPSS version 24 (IBM Inc., Armonk, NY, USA). Statistical significance was set to $P < 0.05$ (two-sided).

Results

A total of 1 128 709 women gave birth in Sweden between 1973 and 1993, 6881 (0.6%) of whom were diagnosed with any type of dementia during the study period, and 654 (0.06%) with vascular dementia, 6488 (0.6%) with dementia and 2161 (0.2%) with Alzheimer's. Some women were registered with more than one diagnosis.

The distribution of the socio-demographic variables within each different type of dementia showed that lower levels of education were more prevalent among women who had been diagnosed with vascular dementia, dementia and Alzheimer's disease. Prior infertility was more common among women who had not been diagnosed with vascular dementia, dementia or Alzheimer's disease (Table 1).

Also, the overall presence of maternal complications such as abruptio placenta, growth restriction, excessive growth, spontaneous preterm labour, gestational diabetes and infertility were all, when not taking the time factor into account, more common among women who had not been diagnosed with any type of dementia, dementia and Alzheimer's disease (Table 2). However, women who had been diagnosed with vascular dementia more often had been diagnosed with pre-eclampsia and pregnancy-induced hypertension compared with women who had not received a vascular dementia diagnosis (Table 2).

Unadjusted Cox proportional hazards models, presented in a supplementary table (Table S1), indicated that high maternal educational level decreases the likelihood of being diagnosed with any type of dementia. Only having delivered girls increased the likelihood of being diagnosed with any dementia and dementia only. Moreover, these unadjusted models indicated that pregnancy-induced hypertension, pre-eclampsia, preterm labour and PPROM were associated with an increased risk of being diagnosed with vascular dementia (Table S1). To further evaluate these associations, models adjusting for socio-demographic variables presented in Table 1, are shown in Table 3. In these models, it was found that having been diagnosed with pregnancy-induced hypertension, pre-eclampsia, preterm labour, PPROM, placental anomaly or pregnancy-induced diabetes increased the likelihood of having been diagnosed with vascular dementia, compared with women who had not been given each of these diagnoses (each diagnosis modelled separately). In addition it was found that each of the cardiovascular diagnoses studied increased the likelihood of having been diagnosed with any dementia, vascular

Table 1. Socio-demographic data on mothers of children born between 1973 and 1993

	Any dementia			Vascular dementia			Dementia			Alzheimer		
	n = 1 121 828 No *n* (%)	*n* = 6881 Yes *n* (%)	*P*-value	*n* = 1 128 055 No *n* (%)	*n* = 654 Yes *n* (%)	*P*-value	*n* = 1 122 221 No *n* (%)	*n* = 6488 Yes *n* (%)	*P*-value	*n* = 112 6548 No *n* (%)	*n* = 2161 Yes *n* (%)	*P*-value
Maternal education												
Elementary/middle	175 164 (15.6)	1873 (27.2)	<0.001	176 811 (15.7)	226 (34.6)	<0.001	174 299 (15.6)	1738 (26.8)	<0.001	176 497 (15.79)	540 (15.7)	<0.001
High school	541 892 (48.3)	3140 (45.6)		544 736 (48.3)	296 (45.3)		542 076 (48.3)	2956 (45.6)		544 066 (48.3)	966 (44.7)	
College/university	378 163 (33.7)	1672 (24.3)		379 708 (33.7)	127 (19.4)		378 234 (33.7)	1601 (24.7)		379 189 (33.7)	646 (29.9)	
Missing	26 609 (2.4)	196 (2.8)		26 800 (2.4)	5 (0.8)		26 612 (2.4)	193 (3.0)		2976 (2.4)	9 (0.4)	
Parity												
Primiparous	249 438 (22.2)	1564 (22.7)	0.326	250 897 (22.2)	105 (16.1)	<0.001	249 504 (22.2)	1498 (23.1)	0.098	250 685 (22.3)	317 (14.7)	<0.001
Multiparous	872 390 (77.8)	5317 (77.3)		877 158 (77.8)	549 (83.9)		872 717 (77.8)	4990 (76.9)		875 863 (77.7)	1844 (85.3)	
Childlessness												
No	1 080 933 (96.4)	6729 (97.8)	<0.001	1 087 020 (96.4)	642 (98.2)	0.014	1 081 317 (96.4)	6345 (97.8)	<0.001	1 985 545 (96.4)	2117 (98.0)	<0.001
Yes	40 985 (3.6)	152 (2.2)		41 035 (3.6)	12 (1.8)		40 904 (3.6)	143 (2.2)		41 003 (3.6)	44 (2.0)	
Origin												
Nordic	995 391 (88.7)	6003 (87.2)	<0.001	1 000 814 (88.7)	580 (88.7)	0.977	995 738 (88.7)	5656 (87.2)	<0.001	999 424 (88.7)	1970 (91.2)	<0.001
Non-Nordic	126 437 (11.3)	878 (12.8)		127 241 (11.3)	74 (11.3)		126 483 (11.3)	832 (12.8)		127 124 (11.3)	191 (8.8)	
Child composition												
Boys and girls	394 474 (35.2)	1505 (21.9)	<0.001	395 872 (35.1)	107 (16.4)	<0.001	394 542 (35.2)	1437 (22.1)	<0.001	395 534 (35.1)	445 (20.6)	<0.001
Only girls	377 509 (33.7)	2740 (39.8)		379 960 (33.7)	289 (44.2)		377 692 (33.7)	2557 (39.4)		379 396 (33.7)	853 (39.5)	
Only boys	349 845 (31.2)	2636 (38.3)		352 223 (31.2)	258 (39.4)		349 987 (31.2)	2494 (38.4)		351 618 (31.2)	863 (39.9)	

Table 2. Maternal pregnancy complications in the study population

	Any dementia			Vascular dementia			Dementia			Alzheimer		
	n = 1 121 828 No *n* (%)	*n* = 6881 Yes *n* (%)	*P*-value	*n* = 1 128 055 No *n* (%)	*n* = 654 Yes *n* (%)	*P*-value	*n* = 1 122 221 No *n* (%)	*n* = 6488 Yes *n* (%)	*P*-value	*n* = 1 126 548 No *n* (%)	*n* = 2161 Yes *n* (%)	*P*-value
Abruptio placenta												
No	1 112 880 (99.2)	6847 (99.5)	**0.005**	1 119 076 (99.2)	651 (99.5)	0.332	1 113 272 (99.2)	6455 (99.5)	**0.009**	1 117 575 (99.2)	2152 (99.6)	**0.047**
Yes	8948 (0.8)	34 (0.5)		8979 (0.8)	3 (0.5)		8949 (0.8)	33 (0.5)		8973 (0.8)	9 (0.4)	
Placental anomaly												
No	1 120 885 (99.9)	6875 (99.9)	0.929	1 127 108 (99.9)	652 (99.7)	**0.050**	1 121 277 (99.9)	6483 (99.9)	0.845	1 125 600 (99.9)	2160 (100.0)	1.000*
Yes	943 (0.1)	6 (0.1)		947 (0.1)	2 (0.3)		944 (0.1)	5 (0.1)		948 (0.1)	1 (0.0)	
Recurrent miscarriages												
No	1 119 989 (99.8)	6868 (99.8)	0.610	1 226 204 (99.8)	653 (99.8)	1.000	1 120 381 (99.8)	6476 (99.8)	0.677	1 124 701 (99.8)	2156 (99.8)	0.439
Yes	1839 (0.2)	13 (0.2)		1851 (0.2)	1 (0.2)		1840 (0.2)	12 (0.2)		1847 (0.2)	5 (0.2)	
Fetal growth restriction (NPR)												
No	1 112 745 (99.2)	6858 (99.7)	**<0.001**	1 118 951 (99.2)	652 (99.7)	0.189*	1 113 136 (99.2)	6467 (99.7)	**<0.001**	1 117 446 (99.2)	2157 (99.8)	**0.001***
Yes	9083 (0.8)	23 (0.3)		9104 (0.8)	2 (0.3)		9085 (0.8)	21 (0.3)		9102 (0.8)	4 (0.2)	
Excessive growth (NPR)												
No	1 120 106 (99.8)	6878 (100.0)	**0.013***	1 126 330 (99.8)	654 (100.0)	0.632*	1 120 499 (99.8)	6485 (100.0)	**0.024***	1 124 823 (99.8)	2161 (100.0)	0.087*
Yes	1722 (0.2)	3 (0.0)		1725 (0.2)	0 (0.0)		1722 (0.2)	3 (0.0)		1725 (0.2)	0 (0.0)	
Pregnancy-induced hypertension												
No	1 101 732 (97.9)	6734 (97.9)	**0.032**	1 107 844 (98.2)	622 (95.1)	**<0.001**	1 102 101 (98.2)	6365 (98.1)	0.533	1 106 352 (98.2)	2114 (97.8)	0.181
Yes	20 096 (1.8)	147 (2.1)		20 211 (1.8)	32 (4.9)		20 120 (1.8)	123 (1.9)		20 196 (1.8)	47 (2.2)	
Pre-eclampsia												
No	1 069 157 (95.3)	6581 (95.6)	0.190	1 075 138 (95.3)	600 (91.7)	**<0.001**	1 069 512 (95.3)	6226 (96.0)	**0.012**	1 073 659 (95.3)	2079 (96.2)	**0.048**
Yes	52 671 (4.7)	300 (4.4)		52 917 (4.7)	54 (8.3)		52 709 (4.7)	262 (4.0)		52 889 (4.7)	82 (3.8)	
Preterm labour and birth												
No	1 063 646 (94.8)	6615 (96.1)	**<0.001**	1 069 634 (94.8)	627 (95.9)	0.226	1 064 016 (94.8)	6245 (96.3)	**<0.001**	1 068 156 (94.8)	2105 (97.4)	**<0.001**
Yes	58 182 (5.2)	266 (3.9)		58 421 (5.2)	27 (4.1)		58 205 (5.2)	243 (3.7)		58 392 (5.2)	56 (2.6)	
PPROM												
No	1 068 365 (95.1)	6624 (96.3)	**<0.001**	1 074 362 (95.2)	628 (96.0)	0.346	1 068 736 (95.2)	6254 (96.4)	**<0.001**	1 072 883 (95.2)	2107 (97.5)	**<0.001**
Yes	53 463 (4.8)	256 (3.7)		53 693 (4.8)	26 (4.0)		53 485 (4.8)	234 (3.6)		54 (2.5)	54 (2.5)	
Gestational diabetes												
No	1 117 254 (99.6)	6865 (99.8)	**0.023**	1 123 467 (99.6)	652 (99.7)	1.000	1 117 645 (99.6)	6474 (99.8)	**0.015**	1 121 960 (99.6)	2159 (99.9)	**0.016**
Yes	4574 (0.4)	16 (0.2)		4588 (0.4)	2 (0.3)		4576 (0.4)	14 (0.2)		4588 (0.4)	2 (0.1)	
Intrauterine fetal death												
No	1 118 924 (99.7)	6871 (99.9)	0.064	1 125 141 (99.7)	654 (100.0)	0.424*	1 119 317 (99.7)	6478 (99.8)	0.098	1 123 635 (99.7)	2160 (100.0)	0.052*
Yes	2904 (0.3)	10 (0.1)		2914 (0.3)	0 (0.0)		2904 (0.3)	10 (0.2)		2913 (0.3)	1 (0.0)	
Infertility												
No	1 095 021 (97.6)	6750 (98.1)	**0.008**	1 101 134 (97.6)	637 (97.4)	0.721	1 095 403 (97.6)	6368 (98.2)	**0.004**	1 099 651 (97.6)	2120 (98.1)	0.136
Yes	26 807 (2.4)	131 (1.9)		26 921 (2.4)	17 (2.6)		16 818 (2.4)	120 (1.8)		26 897 (2.4)	41 (1.9)	

Bold values indicate statistically significant result.
*Fisher's exact test.

Table 3. Hazard ratios for being diagnosed with dementia, vascular dementia, Alzheimer's disease or any dementia adjusted for socio-demographic variables and the presence of any cardiovascular disease

	Any dementia		Vascular dementia		Dementia		Alzheimer's	
	HR** (95% CI)	HR*** (95% CI)	HR** (95% CI)	HR*** (95% CI)	HR** (95% CI)	HR*** (95% CI)	HR** (95% CI)	HR*** (95% CI)
Placenta abruptio								
Yes	0.86 (0.61–1.20)	0.85 (0.61–1.19)	1.06 (0.34–3.30)	1.01 (0.32–3.15)	0.88 (0.62–1.23)	0.87 (0.62–1.22)	0.95 (0.50–1.83)	0.94 (0.49–1.82)
Placental anomaly								
Yes	1.10 (0.50–2.45)	1.07 (0.58–2.38)	3.69 (0.92–14.82)	3.40 (0.85–13.62)	0.97 (0.40–2.34)	0.95 (0.40–2.28)	0.62 (0.09–4.43)	0.61 (0.09–4.34)
Recurrent miscarriages								
Yes	0.98 (0.57–1.70)	0.94 (0.54–1.61)	0.73 (0.10–5.19)	0.64 (0.09–4.59)	0.97 (0.55–1.71)	0.92 (0.52–1.63)	1.14 (0.47–2.73)	1.12 (0.46–2.69)
Fetal growth restriction (NPR)								
Yes	0.79 (0.52–1.19)	0.79 (0.52–1.19)	1.89 (0.47–7.62)	1.87 (0.47–7.54)	0.74 (0.48–1.13)	0.74 (0.48–1.14)	1.13 (0.42–3.02)	1.12 (0.42–3.01)
Excessive growth (NPR)								
Yes	0.54 (0.17–1.66)	0.53 (0.17–1.64)	NA	NA	0.55 (0.18–1.71)	0.54 (0.18–1.69)	NA	NA
Pregnancy-induced hypertension								
Yes	1.26 (1.07–1.48)	1.10 (0.93–1.29)	3.02 (2.12–4.32)	2.15 (1.51–3.08)	1.11 (0.93–1.33)	0.98 (0.82–1.17)	1.30 (0.97–1.74)	1.24 (0.92–1.65)
Pre-eclampsia								
Yes	1.09 (0.97–1.22)	0.98 (0.87–1.10)	2.43 (1.84–3.21)	1.82 (1.38–2.41)	1.00 (0.88–1.13)	0.90 (0.80–1.02)	1.06 (0.85–1.32)	1.01 (0.81–1.26)
Preterm labour and birth								
Yes	1.12 (0.99–1.27)	1.12 (0.99–1.27)	1.80 (1.23–2.66)	1.71 (1.16–2.52)	1.07 (0.94–1.21)	1.07 (0.94–1.21)	1.05 (0.81–1.38)	1.05 (0.80–1.36)
PPROM								
Yes	1.15 (1.02–1.30)	1.14 (1.00–1.29)	1.78 (1.20–2.64)	1.66 (1.12–2.46)	1.10 (0.96–1.25)	1.08 (0.95–1.24)	1.03 (0.78–1.34)	1.02 (0.78–1.33)
Gestational diabetes								
Yes	1.02 (0.63–1.67)	0.78 (0.48–1.28(	3.70 (0.76–12.33)	1.78 (0.44–7.08)	0.92 (0.55–1.56)	0.72 (0.43–1.22)	0.97 (0.24–3.88)	0.89 (0.22–3.57)
Intrauterine fetal death								
Yes	1.14 (0.61–2.12)	1.15 (0.62–2.14)	NA	NA	1.17 (0.63–2.18)	1.18 (0.63–2.20)	1.01 (0.14–7.14)	1.00 (0.14–7.11)
Infertility								
Yes	0.83 (0.70–0.99)	0.80 (0.68–0.96)	1.33 (0.82–2.18)	1.32 (0.81–2.14)	0.81 (0.67–0.97)	0.78 (0.65–0.93)	0.89 (0.65–1.22)	0.90 (0.66–1.23)
Any cardiovascular disease								
Yes	1.86 (1.77–1.96)		5.34 (4.48–6.38)		1.74 (1.66–1.84)		1–26 (1.15–1.38)	
Heart failure								
Yes	2.17 (1.95–2.42)		3.62 (2.85–4.60)		2.04 (1.82–2.92)		1.17 (0.94–1.47)	
Heart disease								
Yes	1.63 (1.50–1.76)		3.09 (2.56–3.72)		1.52 (1.40–1.66)		1.21 (1.04–1.40)	
Atherosclerosis								
Yes	1.47 (1.31–1.66)		3.59 (2.82–4.56)		1.30 (1.14–1.49)		0.87 (0.68–1.12)	

Table 3. (Continued)

	Any dementia		Vascular dementia		Dementia		Alzheimer's	
	HR** (95% CI)	HR*** (95% CI)	HR** (95% CI)	HR*** (95% CI)	HR** (95% CI)	HR*** (95% CI)	HR** (95% CI)	HR*** (95% CI)
Stroke								
Yes	2.94 (2.73–3.17)		10.96 (9.32–12.88)		2.52 (2.32–2.73)		1.76 (1.51–2.04)	
SLE								
Yes	1.75 (1.22–2.51)		2.54 (0.95–6.79)		1.80 (1.25–2.59)		1.47 (0.73–2.94)	
Diabetes								
Yes	1.25 (2.10–2.41)		3.85 (3.22–4.60)		2.11 (1.96–2.28)		1.24 (1.07–1.44)	
Hypertension								
Yes	1.43 (1.35–1.51)		3.43 (2.92–4.02)		1.32 (1.25–1.40)		1.05 (0.96–1.16)	

Each exposure was modelled separately.
**Adjusted for socio-demographic variables presented in Table 1.
***Adjusted for socio-demographic variables presented in Table 1 and the composite variable any cardiovascular disease (presence of either heart failure, heart disease, atherosclerosis, stroke, SLE, diabetes or hypertension).

dementia and dementia. Regarding Alzheimer's disease, an increased likelihood of having been diagnosed with this disease was only found among women who had been diagnosed with ischaemic heart disease, stroke or diabetes (Table 3).

Expanding the models further by including cardiovascular disease as an independent factor in addition to socio-demographic factors, no statistically significant increased risk of non-vascular dementia was found for any of the placental bed disorders studied. However, having been diagnosed with pregnancy-induced hypertension, pre-eclampsia, preterm labour and PPROM was independently associated with an increased likelihood of also having been diagnosed with vascular dementia (Table 3).

Discussion

Main findings

This study of more than 1 100 000 women shows an increased risk of vascular dementia in women with a diagnosis of pregnancy-induced hypertension, pre-eclampsia, spontaneous preterm labour and birth or preterm premature rupture of membranes. This increased risk was attenuated but persisted when adjusted for socio-demographic factors and cardiovascular disease. No statistically increased risk was seen of non-vascular dementia. An increased risk of any kind of dementia was confirmed for several forms of cardiovascular disease.

Strengths and limitations

A strength of this national study is the size. Due to the use of unique personal numbers in Sweden, we were able to cross-link with other registries and control for confounding factors such as socio-demographic strata. Cause of death was also registered. Both inpatients and outpatients were included, but only outpatients in specialist care were available in the registers. In the early stages of vascular dementia, patients may very well be managed in primary care, which is why the risk of vascular dementia and possibly other dementia may be underestimated in this study. The registers have been evaluated and are considered to be of good quality.[18,20–25,27–28,32] The most recent evaluation of the National Patient Register was in 2013, The Medical Birth Register in 2003 and The Cause of Death Register in 2010; the registers from Statistics Sweden were evaluated more recently. However, although the registers are considered to be of good quality, there is always a concern when using ICD-codes from different versions, as a perfect match on a specific diagnosis is not always possible to achieve.

Studying whether placental bed disorders increase the risk of dementia is difficult for a number of reasons. Long-term follow up is necessary, so the comparison of medical records and registries from different periods may lead to

incorrect conclusions, as the criteria for the diagnoses during pregnancy may have varied over time. The criteria for diagnoses of different types of dementia may also be questionable. Many patients suffer from dementia long before diagnosis, which may imply that risks are higher. Also, many suffer from cardiovascular disease long before diagnosis, so adjustment for this confounding factor may not be optimal.

In addition, in the analyses presented, there is always a risk of not including potential confounders, such as physical activity, occupational status and family history of placental bed disorder and/or cardiovascular disease, and it is possible that some of the effects would be attenuated if these factors were included in the models. However, none of these variables was available from the registers included in the present study. Smoking was available but was missing to such a high degree that we chose not to include this variable. Thus, more research on this topic is needed to validate the findings in the current manuscript.

Interpretation

The risk of cardiovascular disease after hypertensive disorders of pregnancy, especially pre-eclampsia, has been thoroughly investigated, but the risk of dementia has been much less studied, and we could only find five relevant articles.

Three articles investigated the association between hypertensive disorders and Alzheimer's disease or dementia. Two of these studies did not find any association, whereas the third, based on death certificates, did find an association with Alzheimer's disease.[11–13] The first two studies have limitations due to their small sample sizes and self-reported pregnancy history.

Two other large studies also found an association with vascular dementia.[14,15] The latter found in addition an association with other forms of dementia, possibly because both inpatients and outpatients were included. Results were attenuated, but the statistical significance remained after having been adjusted for cardiovascular disease.

We found no studies examining the risk of dementia after placental bed disorders.

In our study, we also investigated diagnoses that were not included in the definition of placental bed disorders,[17] such as placental anomalies, recurrent spontaneous miscarriages, infertility and excessive growth. No statistically significant increased risks were seen after any of these diagnoses. The definition of recurrent spontaneous miscarriages in the ICD is vague regarding trimester, and in the original definition of placental bed disorder, only late abortions are included. Further, a lower risk of any dementia was seen in women with infertility and at least one live birth. Not much is published on the issue. Infertility can have many causes and result in various treatments. Our study was not designed to investigate infertility in depth and so other studies will have to be performed to confirm our results, but it is possible that women conceiving after being treated for infertility are healthier than women who did not conceive.

Why is a diagnosis of pregnancy-induced hypertension, pre-eclampsia, spontaneous labour or preterm rupture of membranes independently associated with vascular dementia? Small vessel disease in the brain is linked to cognitive impairment,[33] and is also associated with endothelial function.[34] Endothelial dysfunction is a key factor in pre-eclampsia,[35] and markers for endothelial dysfunction are associated with preterm birth,[36] as well as PPROM.[37] Endothelial dysfunction is impaired in women during the pre-eclamptic episode and several years afterwards.[38]

Levels of circulating angiogenic factors,[39] as well as failure of physiological transformation of the spiral arteries,[40,41] have been linked to spontaneous preterm birth and PPROM. Acute placental atherosis is an arterial lesion present in cases of non-transformed spiral arteries. Atherosis was more common in cases of pre-eclampsia, preterm birth and PPROM than in normal pregnancies.[42] The lesion is similar to the early stages of atherosclerosis and has been claimed to be a better predictor of later cardiovascular disease than pre-eclampsia is.[43]

To elucidate why women with previous placental bed disorder are at increased risk for vascular dementia even when adjusted for cardiovascular disease we would have to follow patients with various forms of the disorder with and without placental atherosis. We would have to investigate degrees of endothelial dysfunction as well as the vessel walls of these women to see whether the development of cardiovascular disease differs in any way from development of cardiovascular disease in women without previous placental bed disorders iin order to discover possible mechanisms. Also, study of early placentation is necessary, but this is more difficult and necessitates an experimental setting.

Conclusions

It is possible that women with placental bed disorders may benefit from screening for early signs of vascular dementia and possibly other types of dementia; at the least, research on the matter may be justified. Early prevention by means of lifestyle changes, as in those with a risk of cardiovascular disease, may be feasible. General practitioners, neurologists and cardiologists have to include questions on course of pregnancy when taking a patient's history.

Acute placental atherosis has been proposed as a surrogate CVD risk marker; if confirmed, this could serve as targeted prevention because early atherosclerosis may be reversible. More information is needed on the long-term

follow up of women with placental bed disorder to investigate how results are related to later disease.

Women with placental bed disorder constitute a risk group for complications during pregnancy and childbirth and also afterwards. The risk of future cardiovascular disease is well known, but the pathophysiological link between placental bed disorders and later dementia has to be further investigated, as it is independent of cardiovascular disease.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

EA was responsible for the conception, planning, carrying out, analysing and writing up of the work. MB took part in the conception, planning and carrying out of the work, and was responsible for analysing and writing up. LM took part in the conception, planning, carrying out, analysing and writing up of the work. GS took part in the conception, planning, carrying out, analysing and writing up of the work.

Details of ethical approval

The study was approved by the research ethics committee at Linkoping university No. 2014/112-31, 26 March 2014.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Unadjusted hazard ratios of being diagnosed with four different types of dementia. ■

References

1 Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ* 2007;335:974.
2 McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J* 2008;156:918–30.
3 Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. *Eur J Epidemiol* 2013;28:1–19.
4 Wu P, Haththotuwa R, Kwok CS, Babu A, Kotronias RA, Rushton C, et al. Preeclampsia and future cardiovascular. Health: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2017;10:1–9.
5 de Bruijn RF, Ikram MA. Cardiovascular risk factors and future risk of Alzheimer's disease. *BMC Med* 2014;12:130.
6 Aukes AM, De Groot JC, Wiegman MJ, Aarnoudse JG, Sanwikarja GS, Zeeman GG. Long-term cerebral imaging after pre-eclampsia. *BJOG* 2012;119:1117–22.
7 Postma IR, Bouma A, Ankersmit IF, Zeeman GG. Neurocognitive functioning following preeclampsia and eclampsia: a long-term follow-up study. *Am J Obstet Gynecol* 2014;211:37.e1–e9.
8 Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol.* 2010;9:689–701.
9 Jokinen H, Lipsanen J, Schmidt R, Fazekas F, Gouw AA, van der Flier WM, et al. Brain atrophy accelerates cognitive decline in cerebral small vessel disease: the LADIS study. *Neurology* 2012;78:1785–92.
10 Aukes AM, Wessel I, Dubois AM, Aarnoudse JG, Zeeman GG. Self-reported cognitive functioning in formerly eclamptic women. *Am J Obstet Gynecol* 2007;197:365.e1–e6.
11 Abheiden CN, van Doornik R, Aukes AM, van der Flier WM, Scheltens P, de Groot CJ. Hypertensive disorders of pregnancy appear not to be associated with Alzheimer's disease later in Life. *Dement Geriatr Cogn Dis Extra* 2015;5:375–85.
12 Nelander M, Cnattingius S, Akerud H, Wikstrom J, Pedersen NL, Wikstrom AK. Pregnancy hypertensive disease and risk of dementia and cardiovascular disease in women aged 65 years or older: a cohort study. *BMJ Open* 2016;6:e009880.
13 Theilen LH, Fraser A, Hollingshaus MS, Schliep KC, Varner MW, Smith KR, et al. All-cause and cause-specific mortality after hypertensive disease of pregnancy. *Obstet Gynecol* 2016;128:238–44.
14 Andolf EG, Sydsjo GC, Bladh MK, Berg G, Sharma S. Hypertensive disorders in pregnancy and later dementia: a Swedish National Register Study. *Acta Obstet Gynecol Scand* 2017;96:464–71.
15 Basit S, Wohlfahrt J, Boyd HA. Pre-eclampsia and risk of dementia later in life: nationwide cohort study. *BMJ* 2018;363:k4109.
16 Staff AC, Redman CW, Williams D, Leeson P, Moe K, Thilaganathan B, et al. Pregnancy and long-term maternal cardiovascular health: progress through harmonization of research cohorts and biobanks. *Hypertension* 2016;67:251–60.
17 Brossens I, Pijnenborg R, Vercruysse L, Romero R. The 'Great Obstetrical Syndromes' are associated with disorders of deep placentation. *Am J Obstet Gynecol* 2011;204:193–201.
18 National Board of Health and Welfare, Centre for Epidemiology. The Swedish Medical Birth Register; A summary of content and quality (Article no. 2003–112-3). Stockholm, Sweden. 2003 [accessed 11 September]. Available from: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/10655/2003-112-3_20031123.pdf.
19 National Board of Health and Welfare, Centre for Epidemiology. Statistics – Health and Medical Care, Pregnancies, Deliveries and Newborn Infants, The Swedish Medical Birth Register 1973–2014, Assisted Reproduction, treatment 1991–2013 (Article No.2015-12-27) Stockholm, Sweden. 2015 [accessed 11 September]. Available from: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/20009/2015-12-27.pdf.
20 Cnattingius S, Ericson A, Gunnarskog J, Kallen B. A quality study of a medical birth registry. *Scand J Soc Med* 1990;18:143–8.
21 National Board of Health and Welfare, Centre for Epidemiology. Kvalitet och innehåll i patientregistret— Utskrivningar från slutenvård 1964–2006 och besök i öppenvård (exklusive primärvårdsbesök) 1997–2006.Stockholm, Sweden. 2008 [accessed 11 September]. Available from: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/8708/2008-125-120081251rev.pdf.
22 National Board of Health and Welfare, Centre for Epidemiology. Kodningskvalitet i patientregistret, Ett nytt verktyg för att mäta

kvalitet. Stockholm, Sweden. 2013 [accessed 11 September]. Available from: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/klassifikationer-och-koder/2013-3-10.pdf.
23 Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;11:450.
24 D'Amico M, Agozzino E, Biagino A, Simonetti A, Marinelli P. Ill-defined and multiple causes on death certificates: a study of misclassification in mortality statistics. *Eur J Epidemiol* 1999;15:141–8.
25 Johansson LA, Westerling R. Comparing Swedish hospital discharge records with death certificates: Implications for mortality statistics. *Int J Epidemiol* 2000;29:495–502.
26 National Board of Health and Welfare, Centre for Epidemiology. Causes of death 2008. Stockholm, Sweden: 2010 [accessed 11 September]. Available from: Retrieved from http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/18014/2010-4-31.pdf.
27 National Board of Health and Welfare, Centre for Epidemiology. Dödsorsaksstatistik Historik, produktionsmetoder och tillförlitlighet. Stockholm, Sweden: 2010. [accessed 11 September]. Available from: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/18019/2010-4-33.pdf
28 Statistics Sweden. Multi-Generation Register 2016; a description of contents and quality. (Serial no. 2017:2.). Örebro, Sweden 2017 [accessed 11 September]. Available from: https://www.scb.se/contentassets/731ea818c63b406a928b9b824ad7f818/ov9999_2016a01_br_be96br1702.pdf
29 Statistics Sweden. Description of the Population in Sweden 2008. Örebro, Sweden. 2009 [accessed 11 September]. Available from: http://www.scb.se/statistik/_publikationer/BE0101_2008A01_BR_BE0109TEXT.pdf
30 Statistics Sweden. Educational attainment of the population 2018. (Publication no. UF 37 SM 1902). Örebro, Sweden. 2019 [accessed 11 September]. Available from: https://www.scb.se/contentassets/c4f928a71e934437b1320762371c35a1/uf0506_2018a01_sm_uf37sm1902.pdf
31 Statistics Sweden. Population and Housing Census 1970 (SOS). Part 12. Report on the planning and processing of the Population and Housing Census 1970. Stockholm, Sweden. 1974.
32 Statistics Sweden. Bortfallsanalys av Utbildningsregistret 2014, Temarapport 2017:5. Örebro, Sweden (2017: [accessed 11 September]. Available from: https://www.scb.se/contentassets/18f5f8f045b8409899fd6600485fa377/uf0506_2016a01_br_a40br1705.pdf
33 Kalaria RN. The pathology and pathophysiology of vascular dementia. *Neuropharmacology* 2018;134(Pt B):226–39.
34 Poggesi A, Pasi M, Pescini F, Pantoni L, Inzitari D. Circulating biologic markers of endothelial dysfunction in cerebral small vessel disease: A review. *J Cereb Blood Flow Metab* 2016;36:72–94.
35 Roberts JM, Lain KY. Recent Insights into the pathogenesis of pre-eclampsia. *Placenta* 2002;23:359–72.
36 Chen X, Scholl TO. Maternal biomarkers of endothelial dysfunction and preterm delivery. *PLoS One* 2014;9:e85716.
37 Ovayolu A, Ovayolu G, Karaman E, Yuce T, Turgut A, Bostancieri N. Maternal serum endocan concentrations are elevated in patients with preterm premature rupture of membranes. *J Perinat Med* 2019;47:510–5.
38 Ostlund E, Al-Nashi M, Hamad RR, Larsson A, Eriksson M, Bremme K, et al. Normalized endothelial function but sustained cardiovascular risk profile 11 years following a pregnancy complicated by preeclampsia. *Hypertens Res* 2013;36:1081–7.
39 Smith GC, Crossley JA, Aitken DA, Jenkins N, Lyall F, Cameron AD, et al. Circulating angiogenic factors in early pregnancy and the risk of preeclampsia, intrauterine growth restriction, spontaneous preterm birth, and stillbirth. *Obstet Gynecol* 2007;109:1316–24.
40 Kim YM, Chaiworapongsa T, Gomez R, Bujold E, Yoon BH, Rotmensch S, et al. Failure of physiologic transformation of the spiral arteries in the placental bed in preterm premature rupture of membranes. *Am J Obstet Gynecol* 2002;187:1137–42.
41 Kim YM, Bujold E, Chaiworapongsa T, Gomez R, Yoon BH, Thaler HT, et al. Failure of physiologic transformation of the spiral arteries in patients with preterm labor and intact membranes. *Am J Obstet Gynecol* 2003;189:1063–9.
42 Kim YM, Chaemsaithong P, Romero R, Shaman M, Kim CJ, Kim JS, et al. The frequency of acute atherosis in normal pregnancy and preterm labor, preeclampsia, small-for-gestational age, fetal death and midtrimester spontaneous abortion. *J Matern Fetal Neonatal Med* 2015;28:2001–9.
43 Staff AC, Dechend R, Redman CW. Review: preeclampsia, acute atherosis of the spiral arteries and future cardiovascular disease: two new hypotheses. *Placenta* 2013;34(Suppl):S73–S78.