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








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Abstract

Aims. To investigate the association between parity and the risk of incident dementia in women.

Methods. We pooled baseline and follow-up data for community-dwelling women aged 60 or older from six population-based, prospective cohort studies from four European and two Asian countries. We investigated the association between parity and incident dementia using Cox proportional hazards regression models adjusted for age, educational level, hypertension, diabetes mellitus and cohort, with additional analysis by dementia subtype (Alzheimer dementia (AD) and non-Alzheimer dementia (NAD)).

Results. Of 9756 women dementia-free at baseline, 7010 completed one or more follow-up assessments. The mean follow-up duration was 5.4 ± 3.1 years and dementia developed in 550 participants. The number of parities was associated with the risk of incident dementia (hazard ratio (HR) = 1.07, 95% confidence interval (CI) = 1.02–1.13). Grand multiparity (five or more parities) increased the risk of dementia by 30% compared to 1–4 parities (HR = 1.30, 95% CI = 1.02–1.67). The risk of NAD increased by 12% for every parity (HR = 1.12, 95% CI = 1.02–1.23) and by 60% for grand multiparity (HR = 1.60, 95% CI = 1.00–2.55), but the risk of AD was not significantly associated with parity.

Conclusions. Grand multiparity is a significant risk factor for dementia in women. This may have particularly important implications for women in low and middle-income countries where the fertility rate and prevalence of grand multiparity are high.

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Introduction

Dementia is one of many disorders with gender differences (Mazure and Swendsen, 2016) and women show a greater prevalence of dementia than men (Winblad *et al.*, 2016). However, longitudinal cohort studies investigating whether the incidence of dementia differs by gender have shown conflicting results. Prospective cohort studies in high-income countries (HIC) such as the USA, the Netherlands and the UK reported no gender differences in the incidence of dementia (Bachman *et al.*, 1993; Paykel *et al.*, 1994; Ruitenberg *et al.*, 2001). On contrary, the 10/66 Dementia Research Group used longitudinal data from six middle-income countries (MIC), including Cuba, the Dominican Republic, Venezuela, Peru, Mexico and China and found that women showed a higher risk of incident dementia than men even after controlling for age, education and occupational attainment (Prince *et al.*, 2012). Higher rates of incident dementia for women in MIC but not HIC may be attributable to the greater gender differences in education, socioeconomic status, lifestyle and health conditions of MIC compared to those of HIC (Medel-Anonuevo, 1995). Pregnancy and childbirth are the most distinctive experiences of women that may change hormone levels, health conditions and lifestyles, and women in MIC have more childbirths on average than women in HIC (United Nations, 2019).

Several studies have shown parity to be associated with the risks for cognitive impairment and dementia. In a case-control study from Germany, the chances of having at least one child and the number of children were both greater among 106 women with Alzheimer's disease (AD) than among 189 women without dementia (Ptok *et al.*, 2002). In a cross-sectional study from China on 4796 postmenopausal women, grand multiparous women (five or more childbirths) showed about 1.3-fold higher risk of cognitive impairment than women with 1–4 parities (Li *et al.*, 2016). In a retrospective analysis on the pooled data of 3549 women from two population-based cohort studies in Korea and Greece, we found that grand multiparous women showed about 1.7-fold higher risk of AD than women with one–four parities (Jang *et al.*, 2018). However, the risk of dementia associated with parity reported from these previous studies employing case-control or cross-sectional designs is subject to various biases; a selection bias (Tripepi *et al.*, 2010) due to the shorter life expectancy of grand multiparous women than women with four parities or less (Hinkula *et al.*, 2006), a prevalence-incidence bias (Hill, 2003) due to the lower mortality from dementia in grand multiparous women than women with four parities or less (Hinkula *et al.*, 2006) and information bias (Tripepi *et al.*, 2010) due to the greater risk of inaccurate information on parity from dementia patients than from cognitively normal elderly individuals.

In this study, we conducted a pooled analysis on the longitudinal data from six population-based prospective cohort studies (four European and two Asian cohorts) to more accurately determine the effect of parity on the risk of incident dementia in older women.

Methods

Study population

We pooled baseline and follow-up data for community-dwelling women aged 60 or older from six members of the Cohort Studies of Memory in an International Consortium (COSMIC) collaboration (Table 1) (Riedel-Heller *et al.*, 2001; Lobo *et al.*,

2011; Sachdev *et al.*, 2013; Dardiotis *et al.*, 2014; Ding *et al.*, 2014; Thorvaldsson *et al.*, 2017; Han *et al.*, 2018). The included cohorts varied in size from 1016 to 6818 participants. From an initial sample of 11 300 women, we excluded 1010 who did not have data on educational level, hypertension, diabetes mellitus (DM) or parity and 534 diagnosed as having dementia at baseline, giving a final sample of 9756 women.

Ethics approval

This study was approved by the University of New South Wales Human Research Ethics Committee (Ref: # HC12446). Each of the six contributing studies had previously obtained ethics approval from their respective institutional review boards and all participants provided informed consent.

Measures

The main outcomes of the present analysis were incident all-cause dementia, AD and non-Alzheimer dementia (NAD). All studies provided data on dementia diagnosis, based on DSM-IV criteria (American Psychiatric Association, 1994) in five studies (Riedel-Heller *et al.*, 2001; Lobo *et al.*, 2011; Dardiotis *et al.*, 2014; Ding *et al.*, 2014; Han *et al.*, 2018) and DSM-III-R criteria (American Psychiatric Association, 1987) in one (Thorvaldsson *et al.*, 2017). Four studies (Dardiotis *et al.*, 2014; Ding *et al.*, 2014; Thorvaldsson *et al.*, 2017; Han *et al.*, 2018) diagnosed AD according to the NINCDS-ADRDA criteria (McKhann *et al.*, 1984) and two studies (Riedel-Heller *et al.*, 2001; Lobo *et al.*, 2011) according to DSM-IV criteria (American Psychiatric Association, 1994). The main exposure was the number of parities. We assigned parity as the number of childbirths in four cohorts and as the number of children in two cohorts. Other data included age, sex, educational level and the presence of hypertension and DM, which were all harmonised when necessary. For the presence of hypertension and DM, we used all available information from a study relevant to diagnoses (medical history record, self-reported history, use of relevant medication and measured blood pressure or glucose level exceeding values indicated by international guidelines).

Analysis

We compared the continuous variables between groups using one-way analysis of variance with Scheffé's post hoc analysis and categorical variables using chi-square tests.

We evaluated the relationship between parity and incident dementia using Cox proportional hazards regression models with time-dependent covariates. We used calendar time as the time axis. The primary outcome was incident dementia and the risk factor of primary interest was the number of parities. Participants who developed dementia during follow-up were censored at the midpoint between their last assessment date when without dementia and their first assessment date when diagnosed with dementia. Participants who remained dementia-free during the follow-up were censored at the most recent assessment date. We initially analysed the number of parities as a continuous variable and estimated hazard ratios (HRs) and 95% confidence intervals (CIs) with unadjusted and adjusted Cox proportional hazards regression models. The adjusted model included age, educational level, hypertension, DM and cohort as covariates. Next, we categorised parity into three strata – no parity (nulliparity), 1–4 parities and five or more parities (grand multiparity) (Babinszki

Table 1. Contributing cohorts

Study	Location	Baseline assessment	Ethnicity	Participants ^a (all/women/included)	Age ^b	Parity ^c
H70	Gothenburg, Sweden	2000–2003	White	1016/787/559	74.7 ± 5.4 (70–92)	2.0 ± 1.6 (0–20)
HELIAD	Larissa and Marousi, Greece	2009–2015	White	1814/1074/896	72.1 ± 5.5 (60–93)	2.0 ± 0.8 (0–7)
KLOSCAD	Nationwide, South Korea	2011–2012	Asian	6818/3919/3496	70.7 ± 7.2 (60–101)	3.6 ± 1.7 (0–12)
LEILA 75+	Leipzig, Germany	1997–1998	White	1265/964/568	81.2 ± 4.9 (75–99)	1.6 ± 1.3 (0–10)
SAS	Shanghai, China	2010–2011	Asian	3141/1873/1772	71.2 ± 8.4 (60–100)	2.0 ± 1.4 (0–9)
ZARADEMP	Zaragoza, Spain	1994–1995	White	4638/2683/2465	74.5 ± 9.6 (60–102)	2.4 ± 1.9 (0–12)

H70, Gothenburg H70 Birth Cohort Studies; HELIAD, Hellenic Longitudinal Investigation of Aging and Diet; KLOSCAD, Korean Longitudinal Study on Cognitive Aging and Dementia; LEILA75+, Leipzig Longitudinal Study of the Aged; SAS, Shanghai Aging Study; ZARADEMP, Zaragoza Dementia Depression Project.

The participants of all studies were randomly sampled.

^aNumbers at the baseline assessment.

^bMean ± standard deviation (range).

^cMean ± standard deviation (range), numbers of children in the H70 and LEILA 75+ and numbers of childbirths in other studies.

et al., 1999) because both grand multiparity and nulliparity have been previously associated with the risk of AD (Ptok *et al.*, 2002; Jang *et al.*, 2018), as well as the risks of medical diseases such as DM and coronary heart disease (Lawlor, 2003; Nicholson *et al.*, 2006). We investigated the association of parity with the risks of AD, and NAD separately. We also analysed the four cohort studies that provided the number of childbirths and the two cohort studies that provided the number of children separately.

The KLOSCAD team harmonised and pooled the dataset and performed the analyses using the Statistical Package for Social Sciences, v20 (SPSS Inc., Chicago, IL).

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request

Results

Of 9756 women dementia-free at baseline, 7010 completed one or more follow-up assessments. The mean follow-up duration was 5.4 ± 3.1 years (Table 2). During the follow-up period, dementia developed in 550 participants (AD in 380 and NAD in 170). Compared to participants who remained dementia-free during follow-up, those who did not complete a follow-up assessment were older and less educated and those who developed dementia were older, had more hypertension and DM and gave more childbirths (Table 3).

Parity as continuous

As shown in Table 4, the risk of dementia increased by 7% for every parity in the adjusted Cox hazard model (HR = 1.07, 95% CI = 1.02–1.13). The risk of NAD increased by 12% for every parity (HR = 1.12, 95% CI = 1.02–1.23), but the risk of AD was not significantly associated with the number of parities (HR = 1.05, 95% CI = 0.99–1.11).

Parity as categorical

Compared to the one–four parities group, grand multiparity increased the risk of dementia by 30% (HR = 1.30, 95%

CI = 1.02–1.67) but nulliparity did not (HR = 0.84, 95% CI = 0.63–1.12). Grand multiparity increased the risk of NAD by 60% (HR = 1.60, 95% CI = 1.00–2.55), but was not associated with the risk of AD. Nulliparity was not associated with the risk of either NAD or AD (Table 4).

When we analysed the four cohort studies that provided the number of childbirths and the two cohort studies that provided the number of children separately, the number of parities was associated with the risk of dementia in both groups, although the association was not statistically significant in the cohorts that provided the number of children (HR = 1.08, 95% CI = 1.02–1.14 for the cohorts providing the number of childbirths; HR = 1.02, 95% CI = 0.91–1.14 for the cohorts providing the number of children).

Discussion

We analysed pooled data for 7010 women older women drawn from six population-based prospective cohort studies, four in Europe and two in Asia. Our results show the number of parities to be associated with the risk of incident dementia. Grand multiparity increased the risk of dementia by 30%, which is comparable to the relative risk of dementia due to some well-known risk factors (1.37 for current/ever smoking (Beydoun *et al.*, 2014), 1.41 for low social participation (Kuiper *et al.*, 2015), 1.33 for midlife obesity (Albanese *et al.*, 2017) and 1.21 for vitamin D deficiency (Shen and Ji, 2015)). Although the association of parity and the risk of dementia in women has been reported by case-control and cross-sectional studies (Ptok *et al.*, 2002; Jang *et al.*, 2018), this is the first prospective study to demonstrate an association between them.

Studies from HIC have reported a similar rate of incident dementia for men and women (Bachman *et al.*, 1993; Paykel *et al.*, 1994; Ruitenberg *et al.*, 2001), but those from MIC showed women to have about 40% higher rates on incident dementia than men, even after controlling for age, educational level and occupational attainment (Prince *et al.*, 2012). In the 1960s MIC had a fertility rate of nearly 6, almost twice that of HIC (United Nations, 2019). Given this, our results suggest that greater rates of incident dementia for women than for men in MIC could be at least partly attributable to high fertility rates and a prevalence of grand multiparity that is over 20% (Mueller *et al.*, 2013; Jang

Table 2. Design and results of follow-up assessments according to cohorts

Study	Follow-up assessments			Numbers with incident dementia			
	Interval (years)	Numbers	Duration ^a	Completers ^b	All	AD	NAD
H70	5	2	8.3 ± 2.3	451	72	42	30
HELIAD	3	1	3.0 ± 0.8	528	26	23	3
KLOSCAD	2	3	4.7 ± 1.6	2873	143	113	30
LEILA 75+	1.5	5	4.5 ± 2.4	568	119	66	53
SAS	5	1	5.0 ± 1.3	900	106	76	30
ZARADEMP	2	2	4.1 ± 1.2	1691	84	60	24

H70, Gothenburg H70 Birth Cohort Studies; HELIAD, Hellenic Longitudinal Investigation of Aging and Diet; KLOSCAD, Korean Longitudinal Study on Cognitive Aging and Dementia; LEILA75+, Leipzig Longitudinal Study of the Aged; SAS, Shanghai Aging Study; ZARADEMP, Zaragoza Dementia Depression Project; AD, Alzheimer dementia; NAD, non-Alzheimer's disease.

^aMean ± standard deviation.

^bNumbers of dementia-free participants at baseline who completed one or more follow-up assessments.

Table 3. Baseline characteristics of the participants

Variable	Followed (N = 7,011)			Statistics ^a		
	A) Remained dementia-free (N = 6,461)	B) Developed dementia (N = 550)	C) Not followed (N = 2,746)	T or χ^2	p	Post hoc
Parity (numbers, mean ± S.D.)	2.6 ± 1.7	2.9 ± 2.1	2.5 ± 1.8	16.771	<0.001	A, C < B
Age at baseline (years, mean ± S.D.)	71.2 ± 7.2	79.8 ± 6.2	73.0 ± 9.0	333.922	<0.001	A < C < B
Education (years, mean ± S.D.)	7.9 ± 4.6	7.0 ± 4.6	7.2 ± 4.9	31.956	<0.001	A > B, C
Hypertension (%)	62.0	73.5	62.7	28.571	<0.001	A, C < B
Diabetes mellitus (%)	15.0	20.2	15.4	10.311	0.006	A, C < B

^aAnalysis of variance with Scheffe's posthoc comparison for continuous variables and chi square tests for categorical variables. The level of significance was considered to be $P < 0.05$.

Table 4. Associations between number of parities and the risk of incident dementia

Model	Dementia	AD	NAD
Numbers of parity ^a	1.07 (1.02–1.13)	1.05 (0.99–1.11)	1.12 (1.03–1.23)
Parity group ^a			
1–4 parities	Referent	Referent	Referent
Nulliparity	0.84 (0.63–1.12)	0.87 (0.61–1.24)	0.80 (0.49–1.30)
Grand multiparity	1.30 (1.02–1.67)	1.20 (0.90–1.61)	1.60 (1.00–1.55)

AD, Alzheimer's disease; NAD, non-Alzheimer's disease.

Values represent hazard ratio with 95% confidence intervals in the parentheses.

^aCox proportional hazards model adjusting for age, educational level, hypertension, diabetes mellitus and cohort.

et al., 2018; Solanke, 2019). Grand multiparity is also likely to be a risk for dementia among women in low-income countries for which the mean fertility rate was 4.6 in 2017 and where grand multiparity is still common (United Nations, 2019).

The association between parity and the risk of incident dementia is potentially explained by a number of mechanisms. First, low high-density lipoprotein (HDL) levels have been associated with the development of dementia (Rasmussen *et al.*, 2015) and AD (Reitz *et al.*, 2010), and parous women were reported to have lower HDL levels than nulliparous women for 3 years after childbirth (Lewis *et al.*, 1996). This appears to be a persistent effect, as a significant trend toward lower HDL levels with increasing parity

has been shown in old age (Humphries *et al.*, 2001). Second, changes in glucose metabolism induced by parity might increase the risk of dementia. We controlled for DM, which is a known risk factor of dementia (Ott *et al.*, 1999). However, higher than average glucose levels in elderly individuals without DM have also been associated with an increased risk of incident dementia (Crane *et al.*, 2013). Insulin sensitivity drops to 50% in the third trimester of pregnancy and grand multiparity is associated with an increased risk of subsequent clinical insulin resistance in premenopausal women (Abdelsalam and Elamin, 2017). It has also been reported that postmenopausal women with four or more children have higher insulin resistance than nulliparous

and primiparous women (Humphries *et al.*, 2001). Third, estrogen has a neuroprotective effect (Barha and Galea, 2010; Inagaki *et al.*, 2010) and low serum bioavailable estradiol has been associated with the risk of cognitive impairment (Yaffe *et al.*, 2000). Since parous women were found to have lower levels of a urinary estradiol metabolite than nulliparous women (Munro *et al.*, 1991; Barrett *et al.*, 2014), and a lower free estradiol index reportedly related to the number of parities in postmenopausal women (Chavez-MacGregor *et al.*, 2008), parity might affect the risk of dementia by exposing women to reduced serum estrogen for much of their adult life. Although these influences of multiparity may increase the risks of both AD and NAD, our results suggest that they may more strongly affect the risk of NAD. Cerebrovascular diseases that are closely associated with lipid and glucose metabolisms are the most common cause of NAD (Rizzi *et al.*, 2014) and vascular dementia was the most common type of incident NAD in the current study.

This study has several strengths compared to previous studies that were case-control or cross-sectional. First, our dataset consists of more than 7000 elderly women from six international population-based cohorts, which is much larger and more representative than the datasets in previous studies. Second, the probability of information bias was relatively low. In case-control and cross-sectional studies, dementia patients with severe cognitive impairment might recall their parity experience incorrectly and it might introduce information bias. However, the current study obtained information on parity when the participants were dementia-free. Lastly, any effect of mortality on the results was also likely to be smaller. Cross-sectional studies assess participants at a single time point and dementia patients with a longer survival rate are more likely to be included than those with a shorter survival rate. Because grand multiparous women show a decreased risk of mortality from dementia (Hinkula *et al.*, 2006), a prevalence-incidence bias might affect the results of cross-sectional studies.

This study also has limitations. Changes in lifestyle and behaviours induced by parity and socioeconomic status which associated with the number of parities could be associated with the risk of incident dementia and have affected our results, and while we controlled for educational level, hypertension, DM and cohort, other confounders might have influenced our outcomes. Adoption or death of children might have distorted parity information because parity data were based on the number of children in two cohorts and the number of childbirths in four cohorts. In addition, the effect of parity on the risk of dementia could be over- or under-estimated because we excluded about one-tenth of participants whose information on educational level, hypertension, DM or parity were not available.

In conclusion, grand multiparity is a significant risk factor for dementia in women. This may have particularly important implications for women in low and middle-income countries where the fertility rate and prevalence of grand multiparity are high.

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Further COSMIC study leaders: Yuda Turana (Atma Jaya Cognitive & Aging Research), Erico Castro-Costa (Bambui Cohort Study of Aging), Bagher Larijani and Iraj Nabipour (Bushehr Elderly Health Program), Kenneth Rockwood (Canadian Study of Health & Aging), Xiao Shifu (Chinese Longitudinal Aging Study), Richard B. Lipton and Mindy J. Katz (Einstein Aging Study), Pierre-Marie Preux and Maëllenn Guerchet (Epidemiology of Dementia in Central Africa), Linda Lam (Hong Kong Memory and Ageing Prospective Study), Ingmar Skoog (Gothenburg H70 Birth Cohort Studies), Toshiharu Ninimiya (Hisayama Study), Richard Walker (Identification and Intervention for Dementia in Elderly Africans study), Hugh Hendrie (Indianapolis Ibadan Dementia Project), Juan J. Llibre-Rodriguez (Cuban Health and Alzheimer Study), Karen Ritchie (Etude Santé Psychologique et Traitement), Kenichi Meguro (Kurihara Study), Martin van Boxtel (Maastricht Ageing Study), Marcia Scazufca (São Paulo Ageing & Health Study), Antonio Guaita (Invecchiamento Cerebrale in Abbiategrosso), Liang-Kung Chen (I-Lan Longitudinal Aging Study), Suzana Shahar (LRGS TUA: Neuroprotective Model for Healthy Longevity among Malaysian Older Adults), Jacqueline Dominguez (Marikina Memory and Aging Project), Murali Krishna (Mysore studies of Natal effects on Ageing and Health), Mary Ganguli (Monongahela Valley Independent Elders Survey), Kaarin J. Anstey (Personality and Total Health Through Life Project), Michael Crowe (Puerto Rican Elderly: Health Conditions study), Mary N. Haan (Sacramento Area Latino Study on Aging), Shuzo Kumagai (Sasaguri Genkimon Study), Tze Pin Ng (Singapore Longitudinal Studies (I)), Henry Brodaty (Sydney Memory and Ageing Study), Kenichi Meguro (Tajiri Project), Richard Mayeux and Nicole Schupf (Washington Heights Inwood and Columbia Aging Project).

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