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Late-Life Risk Factors for All-Cause Dementia and Differential Dementia Diagnoses in Women

A Prospective Cohort Study

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Abstract: Since the first evidence of a decline in dementia incidence was reported in 2011, the focus on modifiable risk factors has increased. The possibility of risk factor intervention as a prevention strategy has been widely discussed; however, further evidence in relation to risk factors is still needed.

The Prospective Epidemiologic Risk Factor (PERF I) study was an observational prospective study of postmenopausal Danish women who were initially examined between 1999 and 2001 (n = 5855). Follow-up data on diagnosis and survival as of December 31, 2014 was retrieved from the National Danish Patient Registry and the National Danish Causes of Death Registry. Cox proportional hazards regression model was applied to calculate adjusted hazard ratios (HR) for selected risk factors for dementia.

Of 5512 eligible subjects, 592 developed dementia within the follow-up period of maximum 15 years. The independent factors associated with increased risk of all-cause dementia were depression (HR = 1.75 [95% CI 1.32–2.34]) and impaired fasting glucose levels. A dose–response relationship was observed between fasting glucose level and risk of dementia with HRs of 1.25 [1.05–1.49] and 1.45 [1.03–2.06] for impaired (5.6–6.9 mmol/L) and hyperglycemic (≥7.0 mmol/L) glucose levels, respectively. The factors associated with a decreased risk of dementia were overweight in late-life (HR = 0.75 [0. 62–0.89]) and physical activity at least once weekly (HR = 0.77 [0.61–0.96]).

The identified risk factors for dementia in women in late-life are all considered modifiable. This supports the notion that prevention strategies may improve the poor future prospects for dementias in the ageing population.

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Abbreviations: AD = Alzheimer disease, APOE = apolipoprotein E, BMI = body mass index, CI = confidence interval, HR = hazard ratio, OD = other/unspecified dementia, PERF = the Prospective Epidemiologic Risk Factor study, VaD = vascular dementia.

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INTRODUCTION

The world's population is ageing. As a result, the prevalence and incidence of dementia has escalated. From the most recent projections, the prevalence and thereby total number of people with dementia is projected to nearly triple by 2050 reaching a total of 131.8 million people worldwide, driven almost entirely by prolonged longevity.[1] Since the first signs of a potential decline in dementia incidence in the United States were published in 2011,[2] followed by several other studies from Europe,[3–5] the possibility of primary prevention by addressing risk factors has been widely discussed.

Risk factors for dementia are divided into the nonmodifiable and modifiable. The nonmodifiable or genetic risk factors include the Apolipoprotein E (APOE) ε4 allele, age, and female sex.[6–8] Many modifiable risk factors have been suggested, but despite extensive research efforts the evidence is inconclusive. In 2010, the National Institutes of Health in the United States stated that results from previous studies were not of sufficient strength to warrant specific recommendations for disease prevention.[9] In 2014, the Alzheimer's Association reached a similar conclusion stating that there is still significant uncertainty with respect to the relationship between individual risk factors and dementia,[10] justifying the need for further studies.

It is estimated that around one-third of Alzheimer disease cases worldwide are caused by 7 modifiable risk factors; low educational attainment, physical inactivity, smoking, midlife hypertension, midlife obesity, diabetes, and depression.[11] Further evidence from the FINGER study, a randomized clinical trial in Finland, suggests that a multidomain interventional approach focusing on several modifiable risk factors can improve or maintain cognitive function in the elderly population.[12]

Our objective was to investigate late-life risk factors for dementia among elderly women. The women comprised the PERF cohort in Denmark, one of the largest individual prospective cohorts of elderly women. The outcome, dementia, was assessed a maximum of 15 years after baseline.

METHODS

Study Population

The Prospective Epidemiologic Risk Factor (PERF I) study was an observational, prospective follow-up study of Danish postmenopausal women. The study participants were identified from a database of subjects who had previously been screened for participation in 1 of 21 clinical randomized controlled trials initiated between 1977 and 1996, including both intervention and nonintervention studies. A total of 8875 women constituted the source population, of which 5855 women gave their written informed consent to participate in the PERF I cohort study. There were no in/exclusion criteria at

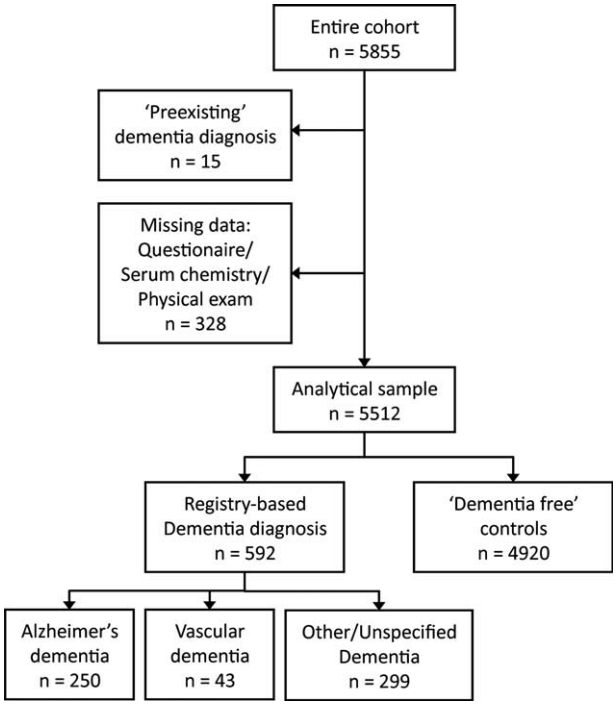

FIGURE 1. Analytical sample for the assessment of risk factors for all-cause dementia and differential dementias: Alzheimer dementia, vascular dementia, and other/unspecified dementias.

the time of enrolment in the observational study. The baseline examination took place between 1999 and 2001 and comprised an interview with completion of a predefined questionnaire, a physical examination, and blood sampling at the study site. The questionnaire was completed by 5847 subjects. Subject's medical history including, but not limited to, history of depression, history of cerebral embolism/hemorrhage, history of hypertension and current treatment, history of diabetes and current treatment and hyperlipidemia and current treatment, were self-reported as part of the questionnaire. The physical examination was completed by 5677 subjects. Vital signs including height, weight measured without shoes but with indoor clothes and blood pressure were measured on calibrated equipment. Blood samples were taken from 5668 subjects and analyzed at a central laboratory. The analytical sample was defined as subjects with no missing data on all relevant variables as illustrated in the flow diagram (Figure 1). The study was carried out in accordance with ICH-GCP with study protocol approval from local ethics committees.

Dementia Endpoint

Follow-up information on dementia status and survival as of December 31, 2014 was retrieved from the National Danish Patient Registry and the National Danish Causes of Death Registry using a unique personal identification number for each subject. The follow-up started on the day of study enrollment and ended at occurrence of event (dementia diagnosis), death, or on December 31, 2014 (retrieval of registry data), whichever came first. Of the entire study population, a total of 651 dementia cases were identified from the registries. Fifteen subjects were excluded from the analysis due to a dementia diagnosis prior to study enrollment. Fifty-five cases were identified based solely on their cause of death in the National Danish Causes of Death Registry, since they were not diagnosed with dementia according to the National Danish Patient Registry. The remaining subjects (n = 581) had a diagnosis of dementia in the National Danish Patient Registry leading to a total of 636 incident dementia cases prior to identification of the analytical sample. Dementia diagnoses were classified according to the International Classification of Diseases, 10th revision (ICD10). The following codes were considered a dementia diagnosis: ''OD'' (dementia in other diseases classified elsewhere; unspecified dementia and senility) [F02-F03 and R54, n = 325], ''AD'' (dementia in Alzheimer disease, other degenerative diseases of the nervous system) [F00 and G30–G32, n = 264], and ''VaD'' (vascular dementia) [F01, n = 47].

Statistical Analysis

Statistical analyses were conducted using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium) and SAS version 9.4 (SAS Institute Inc, Cary, NC).

Baseline characteristics of controls and subjects found to have dementia at follow-up were compared using a one-way analysis of variance (ANOVA) for quantitative variables and χ^2 test for comparison of categorical variables (Table 1).

A Cox proportional hazards regression model was used to assess the selected risk factors in an age-adjusted and a multivariate adjusted regression analysis, the follow-up time since baseline was used as time scale. Age was included as continues variable and risk estimates reported pr. 5 years of aging. In the multivariate model, the categorical variables education level (primary school, high school, or university), body mass index (BMI, kg/m^2) where underweight was <18.5, normal weight $\geq 18.5 < 25$, overweight $\geq 25 < 30$, and obese ≥ 30, smoking (never, past, or current), alcohol consumption (never, <10.5 alcohol units/week, 10.5–21 alcohol units/week, or >21 alcohol units/week), physical activity (other than walking) (never, once weekly, twice weekly, or 3 or more times per week), history of depression (yes/no), history of cerebral embolism/hemorrhage (yes/no), systolic blood pressure >160 mm Hg, fasting glucose levels (normal <5.6 mmol/L, impaired 5.6–6.9 mmol/L, or hyperglycemic ≥ 7.0 mmol/L) and total cholesterol levels >6.5 mmol/L and age as a continuous variable were included. Subjects who reported treatment for hypertension, diabetes, or hyperlipidemia at baseline were included in the hypertensive (systolic blood pressure >160 mm Hg), hyperglycemic (fasting glucose ≥ 7.0 mmol/L), or hyperlipidemic (total cholesterol levels >6.5 mmol/L) groups, respectively. Regression analysis was performed for all-cause dementia and separate analyses for differential diagnoses (OD, AD, and VaD). Due to a large proportion of missing data from 781 subjects, the family history of dementia (yes/no) was not included in the multivariate analysis.

RESULTS

Baseline Characteristics

Of the analytical sample (n = 5512), a total of 592 dementia cases were identified from the registries during the follow-up period (Table 1). The maximum follow-up period was 15 years (mean follow-up: 11.9 ± 3.9 years) starting on the day of study enrollment and ending at occurrence of event (dementia

TABLE 1. Demographic Characteristics by Dementia Status of the Analytical Sample at Baseline

Variable	Dementia-Free Controls n = 4920	All-Cause Dementia n = 592	Alzheimer's Dementia n = 250	Vascular Dementia n = 43	Other/ Unspecified Dementia n = 299	P-value All-cause dementia vs. control	P-value Differential diagnosis vs. control
Age, mean ± SD, yr	70.1 ± 6.4	75.1 ± 5.3	74.4 ± 4.9[*,†]	74.3 ± 5.8[*]	75.8 ± 5.5[*,‡]	<0.001	<0.001
All-cause deaths until December 31, 2014, n (%)	1388 (28)	386 (65)	141 (56)	27 (63)	218 (73)	<0.001	<0.001
Education, n (%)							
Primary school	3496 (71)	437 (74)	186 (74)	36 (84)	215 (72)		
High school	1072 (22)	111 (19)	44 (18)	6 (14)	61 (20)	0.2	0.4
University	352 (7)	44 (7)	20 (8)	1 (2)	23 (8)		
BMI, mean ± SD, kg/m^2	26.2 ± 4.2	25.8 ± 4.2	25.8 ± 4.2	26.8 ± 5.4	25.7 ± 4.1	0.06	0.1
Smoking, n (%)							
Never	2334 (47)	284 (48)	129 (52)	14 (33)	141 (47)		
Past	1477 (30)	196 (33)	72 (29)	16 (37)	108 (36)	0.09	0.04
Current	1109 (23)	112 (19)	49 (20)	13 (30)	50 (17)		
Alcohol consumption, n (%)							
Never	2115 (43)	282 (48)	122 (49)	14 (33)	146 (49)	0.2	0.3
<10.5 alcohol units/week	1174 (24)	134 (23)	58 (23)	13 (30)	63 (21)		
10.5–21 alcohol units/week	1283 (26)	142 (24)	58 (23)	12 (28)	72 (24)		
>21 alcohol units/week	348 (7)	34 (6)	12 (5)	4 (9)	18 (6)		
Physical activity							
None	1469 (30)	227 (38)	81 (32)	22 (51)	124 (42)	<0.001	<0.001
1 time/week	1049 (21)	118 (20)	48 (19)	8 (19)	62 (21)		
2 times/week	639 (13)	74 (13)	35 (14)	4 (9)	35 (12)		
3+ times/week	1763 (36)	173 (29)	86 (34)	9 (21)	78 (26)		
Systolic blood pressure >160 mm Hg or treated hypertension (self-reported)	1852 (38)	275 (47)	103 (41)	20 (47)	152 (51)	<0.001	<0.001
History of cerebral embolism/hemorrhage (self-reported)	142 (3)	28 (5)	10 (4)	1 (2)	17 (6)	0.02	0.04
Fasting glucose							
Normal (<5.6 mmol/L)	3181 (65)	349 (59)	146 (58)	25 (58)	178 (60)	0.02	0.3
Impaired (5.6–6.9 mmol/L)	1486 (30)	206 (35)	89 (36)	15 (35)	102 (34)		
Hyperglycemic (≥7.0 mmol/L) or treated diabetes (self-reported)	253 (5)	37 (6)	15 (6)	3 (7)	19 (6)		
Total cholesterol (>6.5 mmol/L) or treated hyperlipidemia (self-reported)	2138 (44)	287 (49)	125 (50)	20 (47)	142 (48)	0.02	0.2
History of depression (self-reported)	307 (6)	52 (9)	12 (5)	4 (9)	36 (12)	0.02	0.0006
History of other neural disorders (self-reported)[§]	1601 (33)	229 (39)	92 (37)	22 (51)	115 (50)	0.003	0.006

[*] Significant difference ($P < 0.05$) from dementia-free controls (pairwise comparison using Student–Newman–Keuls test).
[†] Significant difference ($P < 0.05$) from other/unspecified subgroup (pairwise comparison using Student–Newman–Keuls test).
[‡] Significant difference ($P < 0.05$) from Alzheimer disease subgroup (pairwise comparison using Student–Newman–Keuls test).
[§] Other neural disorders include chronic headache, eye disorders, disabled hearing, and epilepsy.

diagnosis), death, or on December 31, 2014 (retrieval of registry data), whichever came first.

The dementia groups (AD, VaD, and OD) were characterized as being markedly older than dementia-free controls (74.4–75.8 versus 70.1 years, $P < 0.001$). The proportion of deceased subjects in each dementia group was markedly higher than in the dementia-free control group. No differences were observed in education levels ($P = 0.2$), BMI ($P = 0.06$), smoking habits ($P = 0.09$), and alcohol consumption ($P = 0.2$) when comparing all-cause dementia with dementia-free controls. The dementia groups are characterized by a larger proportion of subjects with elevated blood pressure ($P < 0.001$) and a larger proportion of physically inactive subjects ($P < 0.001$). When comparing the differential groups with the dementia-free controls, smoking habits, physical activity, elevated blood pressure, history of cerebral embolism/hemorrhage, history of depression, and other neural disorders were significantly different. No significant differences were observed in the proportion of subjects with hyperlipidemia between the differential dementia groups and the dementia-free controls ($P = 0.2$).

Risk Factors for All-Cause Dementia

The overall incidence of dementia in the analytical sample was 8.9 (8.3–9.7) per 1000 person years. The age-specific incidence rates increased with increasing age ranging from 0.9 (0.3–2.7) per 1000 person years in the youngest age group (<60) to 28.0 (23.4–33.6) per 1000 person years in the oldest age group (≥80). The incidence approximately doubled every 5 year (data not shown).

A Cox proportional hazards regression model was used to assess HRs for selected risk factors as listed in Table 2.

Age was a strong risk factor for all-cause dementia and for differential diagnoses. From an age-adjusted model, physical activity (other than walking) at least once a week and overweight were associated with decreased risk of all-cause dementia, while depression and higher levels of fasting glucose (≥5.6 mmol/L) were associated with an increased risk of dementia (see Table 1, Supplemental Content, which contains the results from the age-adjusted model, http://links.lww.com/MD/A780).

In the multivariate analysis the independent factors associated with increased risk of dementia were depression, impaired fasting glucose levels (5.6–6.9 mmol/L), and hyperglycemia (>6.9 mmol/L or treated diabetes). The factors associated with a decreased risk were overweight and physical activity (other than walking) at least once a week. Obesity as defined by a BMI ≥30 was not associated with the development of dementia (Table 2).

No major differences were observed between the age-adjusted and the multivariate-adjusted models.

Risk Factors for Differential Dementia Diagnosis

The risk factor profiles for differential diagnoses of dementia were generally similar but certain risk factors were notably different between the AD, VaD, and OD groups (Table 2). The age-adjusted models revealed that family history of dementia was associated with an increased risk of AD but no association was observed for VaD and OD. Impaired fasting glucose levels were solely associated with AD in the multivariate adjusted model, increasing the risk by 33% compared with normal glucose levels. Being overweight had a negative association with both AD and OD, lowering the risk by 28% and 25% respectively in the multivariate analysis. Physical activity at least 3 times per week was associated with a decreased risk of VaD (58%) and OD (29%) compared with those being physically inactive (apart from walking). Smoking increased the risk of VaD, in which the risk was 156% higher than in subjects who had never smoked. Depression increased the risk for OD with a similar magnitude as smoking did for VaD. No association was observed between depression and AD or VaD in either of the regression models (Table 2).

DISCUSSION

Using public health registries we were able to follow subjects for up to 15 years from baseline, providing an excellent opportunity to study potential risk factors in a large sample of elderly women. To our knowledge, this is one of the largest individual prospective cohort studies to investigate risk of all-cause dementia and differential dementia diagnoses in late-life.

Equal to our findings, other large cohort studies (including the EURODEM collaboration) have found incidence rates of dementia for women comparable to what we found in the PERF cohort.[7,13,14]

The factors associated with an increased risk of all-cause dementia were increasing age, physical inactivity, depression, and impaired glucose levels. Being overweight in late-life was protective against development of all-cause dementia when compared with women with a normal BMI. The differential diagnoses of dementia shared several risk factors. Smoking and depression were solely associated with a higher risk of developing VaD and OD, respectively.

Our results suggest that overweight in women (mean age 70.7, SD 6.5) has a protective relation to development of all-cause dementia, AD, and OD. Overweight and obesity have previously been linked to dementia in both midlife and late-life. A BMI in midlife indicating overweight or obesity has often been proposed to increase risk of developing dementia in later life.[15,16] Evidence suggests that the association between overweight/obesity and dementia vanish later in life.[15] A study in late-life from the Kungsholmen cohort in Sweden (mean age 80.8, SD 4.5) showed, separately for both men and women, a similar negative relationship between high BMI and development of dementia as we found in our study.[17] The CAIDE study in Finland also showed a negative association between high BMI in late-life and development of dementia.[18] Contradictorily, a retrospective cohort study involving nearly 2 million men and women in the UK recently disproved the hypothesis that obesity in midlife could increase the risk of dementia in later life and actually strengthened the evidence that overweight and obesity may protect against dementia in later life.[19]

The CAIDE study also showed that a decrease in BMI from mid- to late-life and a low late-life BMI of $<25\ kg/m^2$ (mean age, 71.2, SD 4.0) are associated with higher risk of all-cause dementia and AD.[18] We have also previously shown an association between changes in body fat mass and cognitive impairment in elderly women.[20] The relationship is however unlikely to be causal since weight loss is known to occur with comorbidities in late-life, and is therefore often linked to poor health and mortality.[21] In addition, BMI is known to have several limitations as a health measure,[22] wherefore a simple measure like waist circumference would have been of interest in the evaluation of bodyweight and body composition in relation to dementia.

Among the lifestyle factors studied, only physical inactivity had an association with increased risk of all-cause dementia. Physical activity at least once weekly reduced the risk of all-cause dementia by 20% to 23% compared with physical

TABLE 2. Multivariate-Adjusted Hazard Ratios (HRs) for Risk Factors Associated With All-Cause Dementia and Differential Dementia Diagnoses

	All-Cause Dementia		Alzheimer's Disease		Vascular Dementia		Other/ Unspecified Dementia	
Variable	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Demographics								
Age (per 5 years of ageing)	2.05	1.89–2.21	1.92	1.71–2.15	1.85	1.41–2.43	2.32	2.07–2.60
Education								
Primary school	Reference							
High school	0.91	0.74–1.13	0.84	0.60–1.17	0.52	0.22–1.26	1.05	0.78–1.40
University	0.91	0.66–1.25	0.98	0.61–1.57	0.23	0.03–1.67	0.96	0.62–1.50
BMI								
<18.5 (underweight)	0.88	0.45–1.72	0.92	0.34–2.51	no data		0.93	0.38–2.28
≥18.5 <25 (normal)	Reference							
≥25 <30 (overweight)	0.75	0.62–0.89	0.72	0.54–0.96	0.68	0.33–1.40	0.75	0.58–0.98
≥30 (obese)	0.79	0.62–1.01	0.74	0.51–1.09	1.28	0.57–2.86	0.75	0.52–1.06
Lifestyle								
Smoking								
Never	Reference							
Past	1.14	0.95–1.37	0.93	0.70–1.25	1.71	0.83–3.54	1.28	0.99–1.65
Current	1.13	0.90–1.41	1.08	0.77–1.51	2.56	1.18–5.55	1.04	0.74–1.44
Alcohol								
Never	1.09	0.89–1.35	1.12	0.82–1.53	0.53	0.25–1.13	1.19	0.89–1.61
<10.5 alcohol units/week	Reference							
10.5–21 alcohol units/week	0.97	0.76–1.23	0.91	0.63–1.32	0.90	0.41–2.00	1.03	0.73–1.45
>21 alcohol units/week	0.97	0.67–1.42	0.81	0.43–1.52	1.13	0.36–3.50	1.07	0.63–1.82
Physical activity								
None	Reference							
1 time/week	0.77	0.61–0.96	0.84	0.58–1.20	0.55	0.24–1.25	0.76	0.56–1.04
2 times/week	0.80	0.61–1.04	0.99	0.66–1.47	0.46	0.16–1.35	0.72	0.49–1.05
3+ times/week	0.79	0.64–0.97	1.00	0.73–1.37	0.42	0.19–0.93	0.71	0.53–0.95
Vascular								
Systolic blood pressure >160 mm Hg or treated hypertension	1.05	0.89–1.24	0.89	0.69–1.16	1.16	0.62–2.16	1.18	0.93–1.49
History of cerebral embolism/hemorrhage	1.28	0.88–1.88	1.17	0.62–2.22	0.57	0.08–4.20	1.43	0.87–2.34
Fasting glucose/diabetes								
Normal (<5.6 mmol/L)	Reference							
Impaired (5.6–6.9 mmol/L)	1.25	1.05–1.49	1.33	1.02–1.74	1.23	0.63–2.36	1.20	0.94–1.54
Hyperglycemic (≥7.0 mmol/L) or treated diabetes	1.45	1.03–2.06	1.56	0.90–2.69	1.35	0.39–4.71	1.47	0.91–2.39
Total cholesterol (>6.5 mmol/L) or treated hyperlipidemia	1.12	0.95–1.32	1.19	0.93–1.53	1.09	0.60–2.00	1.07	0.85–1.34
Neural disorders								
History of depression (yes/no)	1.75	1.32–2.34	0.96	0.53–1.71	1.86	0.66–5.26	2.58	1.82–3.68
History of other neural disorders (yes/no)	0.99	0.83–1.17	0.97	0.75–1.27	1.67	0.91–3.08	0.93	0.73–1.18

All HRs listed in the table were mutually adjusted.

inactivity. For the differential diagnoses of dementia, physical inactivity was associated with risk of VaD and OD. The causal relation between physical activity and dementia is uncertain and some suspect the length of the follow up period may have biased some of the previous findings.[23] A study of physical activity in late-life from the Rotterdam cohort put follow-up time into perspective.[24] The investigators suggest that physical activity has an inverse relationship with dementia onset during up to 4 years of follow-up, after which the protective effect diminishes. They speculate this may either be related to reverse causation or a short-term effect of physical activity.[24] An increase in physical activity after midlife recently was shown to protect against both all-cause dementia and AD,[25] supporting the association observed in the current study.

Smoking was not related to all-cause dementia in our cohort. However, in the analysis of differential diagnoses, current smoking was associated with an increased risk of VaD. Pathologically, this makes sense since smoking is a strong risk factor for both cerebrovascular and cardiovascular diseases. Smoking is involved in atherosclerosis, causing narrowing of blood vessels in the brain. In addition, smoking has been shown to have both a direct, affecting the folding of amyloid β, and an indirect detrimental effect in relation to dementia.[26,27]

Depression increased the risk of all-cause dementia and OD. Evidence from the literature is consistent with our findings where late-life depression has been associated with the development of dementia.[28,29] The most recent meta-analyses, one in the 2014 World Alzheimer's Report[3] and another from Diniz et al,[30] reported increased risks of 97% and 85% respectively. In the present study, the risk of developing all-cause dementia increased by 75% in elderly women with a history of depression, compared with subjects who had never suffered from the illness. The causal relationship between depression and dementia is however unclear. In the current study, we have no information about the onset of depressive symptoms. In the case of late-life onset, the observed association could potentially be a result of reverse causation.

There is somewhat more limited evidence when it comes to depression and risk of differential dementia diagnoses. In the current study, we found an association with OD (HR 2.58 (95% CI 1.82–3.68), while no association was observed with AD and VaD. Barnes et al[28] studied all-cause dementia, AD, and VaD and found associations between both AD and VaD for subjects with either late-life depressive symptoms or subjects with both midlife and late-life symptoms. The review from Diniz et al[30] suggests similar associations in their pooled estimates with the strongest association between depression and VaD. The missing association with AD in the current study may be caused by misclassification of subjects in the OD group—a heterogeneous group that is likely to contain several subjects with AD and mixed pathologies.

Our findings suggest a potential dose–response relationship between fasting glucose levels and risk of all-cause dementia when measured in late-life. The risk of all-cause dementia was increased by 25% and 45% in the impaired and hyperglycemic groups, respectively. The association between self-reported diabetes and risk of dementia did not confirm this relation, a potential result of under diagnosis which has been estimated to be up to 46% worldwide.[31] In relation to diabetes increased risks of 50% and 58% have previously been reported in the Kungsholmen Study and the French Three-City Study.[32,33] Contrarily, the Three-City Study found no association between impaired fasting glucose and dementia only with diabetes.

STRENGTHS AND LIMITATIONS

The follow-up information derived from registry data is uniquely available in Denmark where all contacts with primary care have been registered since 1977. This results in very limited loss to follow-up and all subjects can be followed up until time of death. We studied a large group of elderly women in Denmark, a homogenous population where generalization to other population is not obvious. The cohort only comprised women and therefore generalization cannot be made to men of similar ages. It is well known that women are at higher risk for developing dementia and although some risk factors are likely to be determined by the population in study, the HRs from Cox proportional-hazard analysis were comparable to associations found in similar cohorts making the generalization more likely.

Among the limitations of the study is the missing Apolipoprotein E (APOE) assessment. The APOE ε4 allele is a major genetic risk factor for AD.[6] Further, we did not include any measures of cognitive performance or activities of daily living at baseline in this analysis, and since we did not have screening for dementia using a standard diagnostic criteria at baseline it is possible that some of the dementia cases had prodromal disease already at baseline eventually affecting the cause and effect relationship. Risk factors assessed in the analysis were selected based on the available data and evidence from the literature. No measures of nutrition or information on diet were obtained at baseline. These factors have previously been suggested as risk factors for dementia and could potentially introduce residual confounding in our analysis.[34,35]

Epidemiological study designs such as that of the PERF I study may introduce selection bias by possible over-representation of relatively healthy subjects in the cohort. Participants in the PERF I study were recruited by active recruitment from the CCBR Clinical Research subject database, a recruitment method that could lead to above-mentioned selection bias. It should however be noted that their where no in- or exclusion criteria's at the time of enrolment, which could potentially reduce the risk of selection bias.

In relation to differential diagnosis the method with registry-linkage may have reduced the accuracy of the actual diagnosis. Differential dementia diagnoses are difficult since many patients have a mixed pathology making a diagnosis of 1 specific type of dementia difficult.[36] Another ongoing problem is under-diagnosis of dementia in primary care which has been reported to be more than 50% in the United Kingdom.[37] The under-diagnosis could have biased our analysis, but would eventually drive the results toward the null hypothesis.

In conclusion, we assessed some of the most widely studied risk factors for dementia in late-life. We found the factors associated with an increased risk of all-cause dementia were physical inactivity, depression, and impaired fasting glucose. A protective relationship was found for overweight (BMI 25–29.9), as compared with normal weight women. These risk factors are all considered modifiable and therefore provide further evidence that prevention strategies could be a way to counteract the otherwise poor future prospects for dementia in the ageing population.

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