Received: 9 September 2020 | Revised: 23 November 2020 | Accepted: 24 November 2020

DOI: 10.1002/alz.12279

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Sex differences in dementia and response to a lifestyle intervention: Evidence from Nordic population-based studies and a prevention trial

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Abstract

Introduction: Evidence on sex differences in the risk for dementia has been mixed. The goal was to assess sex differences in the development of dementia, and in the effects of a lifestyle intervention.

Methods: Two strategies were adopted, one using combined data from three large Nordic population-based cohort studies (n = 2289), adopting dementia as outcome, and 2-year multidomain lifestyle intervention (n = 1260), adopting cognitive change as outcome.

Results: There was higher risk for dementia after age 80 years in women. The positive effects of the lifestyle intervention on cognition did not significantly differ between men and women. Sex-specific analyses suggested that different vascular, lifestyle, and psychosocial risk factors are important for women and men in mid- and late-life.

Conclusion: Women had higher risk for dementia among the oldest individuals. Lifestyle interventions may be effectively implemented among older men and women.

KEYWORDS
cohort study, dementia, lifestyle intervention, risk factors, sex differences

1 | BACKGROUND

Dementia is the leading cause of disability and institutionalization, and it shortens survival among older adults. Globally, two thirds of individuals living with dementia and Alzheimer's disease (AD) are women.[1] Both higher prevalence and incidence of dementia have been reported in women compared to in men,[2–4] and this is exacerbated among older adults above the age of 80 years.[3,5–8] Although several hypotheses have been postulated, the reasons underlying these discrepancies are not yet fully understood.[9–11]

Worldwide, women have a higher life expectancy than men[12,13] and this has been hypothesized to contribute to the sex differences in dementia prevalence and incidence. However, this may not fully account for the sex differences in dementia occurrence, especially as the life expectancy gap in developed countries has been narrowing in the last decades.[14]

Various vascular, metabolic, and lifestyle factors have been associated with the risk for dementia. These include low education, hypertension, diabetes, unhealthy diet, physical inactivity, hormone replacement therapy, and psychosocial factors such as cohabitant status and hopelessness.[15,16] It has also been reported that the apolipoprotein E (*APOE*) ε4 genetic risk factor may have a larger impact on dementia risk among women.[17–19] While there may be sex differences in the prevalence of these factors,[20–23] it is still unclear whether these factors are differentially associated with the risk for dementia.[23] In many previous cohort studies, restricted sample size (especially for men) has limited the potential for sex-specific analyses.

It has also been suggested that a proportion of the sex differences may be attributed to cognitive reserve (the capacity to preserve cognitive performance in the presence of brain pathology),[24] as men tended to have higher levels of education and more mentally stimulating occupations, which are protective against dementia.[25,26] Similarly, brain reserve (having higher quantities of neurobiological substrates/measures (e.g., brain volume, synapses, neurons), which allows for optimal cognitive performance in the presence of brain pathology), was assumed to play a role, because men tend to have larger cerebral brain volume, head size, and hippocampal volume, although these differences do not necessarily reflect the rate of cognitive decline.[27,28]

Considering that many of the aforementioned dementia risk factors are modifiable, multidomain lifestyle interventions have been conducted to alter such risk factors (e.g., diet, exercise, vascular risk factors), and reduce the risk for dementia. Although the prevalence of risk factors may differ among men and women, little is known about whether women and men recruited into such interventional trials have different risk profiles, and whether they show different responses to the intervention.

The overall goal of the study was to assess sex differences in dementia, and sex differences in the response to a lifestyle intervention to prevent dementia. To address the first aim, joint data were used from population-based cohort studies to: (1) assess whether the risk for dementia differs between women and men and (2) investigate whether the association between dementia risk factors and dementia differs between women and men. To address the second aim, we used data from a multidomain lifestyle intervention trial to: (1) examine whether the response to a lifestyle intervention measured as cognitive change differs between women and men and (2) study whether the reported experiences of the lifestyle intervention differed between women and men.

RESEARCH IN CONTEXT

1. **Systematic review:** Although many studies have investigated whether there are sex differences in the development of dementia, and various hypotheses have been postulated, the evidence remains mixed. The goal of this study was to assess the sex differences in the development of dementia, and in the effects of a lifestyle intervention. The study used data from three population-based cohort studies and the 2-year FINGER multidomain lifestyle intervention.
2. **Interpretation:** Women and men did not significantly differ in their risk for dementia across all age groups, but women showed a higher risk after age 80 years. Sex-specific analyses suggested that different vascular, lifestyle, and psychosocial risk factors are important for women and men in mid- and late-life. FINGER had positive intervention effects for both sexes.
3. **Future directions:** It will be important for future studies to further investigate the underlying mechanisms, including hormonal changes and cognitive reserve, while using a life-course approach.

2 | METHODS

Two strategies were adopted, one using combined data from three large Nordic population-based cohort studies (n = 2289) adopting dementia as outcome, and a 2-year multidomain lifestyle intervention (n = 1260) adopting cognitive change as outcome.

2.1 | Population-based cohort studies

The three population-based studies included were the following. (1) The Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study conducted in Finland. Participants were first examined at mid-life (age range: 40–64) in the North Karelia Project and the Finnish part of the World Health Organization MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) project, the FINMONICA study, with baseline assessments in one of the following years: 1972, 1977, 1982, or 1987. The first re-examination took

place in 1998, and the second re-examination in 2005 to 2008. (2) The Gothenburg H70 Birth Cohort Studies, which started in the early 1970s to study health and health-related conditions in an older population in Gothenburg, Sweden. Data were used from the cohort born 1930, examined at ages 70 (in 2000–2001), 75 (in 2005–2006), and 79 (in 2009–2010). (3) The Kungsholmen Project (KP) was conducted among adults 75+ years of age (age range: 75–95) residing in Kungsholmen district, Stockholm, Sweden. Individuals born before 1913 and living in Kungsholmen were invited to participate in the initial examination, which took place from 1987 to 1989. All three studies comply with the Declaration of Helsinki, and the respective local ethics committees approved each study. All participants provided written informed consent. All studies were previously described in more detail,[29–31] including a similar multi-center approach.[32]

2.2 | Dementia diagnosis

In all three cohort studies, the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (DSM-IV in CAIDE; DSM-III-R in H70 and KP) were used to diagnose dementia. Interviews were also performed with close informants for information on participants' cognition. The clinical phase involved (but was not limited to) detailed neurological, neuropsychological, neuropsychiatric, and cardiovascular examinations and interviews/questionnaires on participant/family history and lifestyle factors.[29,31,33]

For analyses with long follow-up (CAIDE study), in addition to dementia assessments and diagnoses within the CAIDE study, dementia diagnoses were included from the National Hospital Discharge Register, which provides information on inpatients at public hospitals, as well as the Drug Reimbursement Register and Causes of Death Register. Diagnoses in both the National Hospital Discharge Register and the Causes of Death Register are defined using International Classification of Diseases (ICD) codes.

2.3 | Other measures

In all three studies, baseline assessments were standardized and adhered to international guidelines. Re-examination surveys were comparable to baseline surveys, including a medical exam, personal interviews/questionnaires on sociodemographic factors, health status, medical history, health- and psychological-related factors. The factors selected for this study are listed in Tables 1 and 2.

TABLE 1 Sociodemographic and clinical characteristics of participants in the three included studies for short follow-up analyses: CAIDE, H70, and KP

Short follow-up (all data)				
	N	Women (n = 1596)	Men (n = 693)	*P*-value
Dementia cases	2289	371 (16.2%)	95 (4.2%)	<**0.001**
Baseline age (range 65–101)	2289	76.0 (6.9)	73.6 (6.0)	<**0.001**
Age > 80 years at follow-up	2278	861 (76.3%)	730 (63.5%)	<**0.001**
Follow-up time	2278	6.0 (2.5)	6.5 (2.4)	<**0.001**
Education (range 0–48)	1633	0–7 years: 439 (54.7%) 8–14 years: 340 (42.3%) 14+ years: 24 (3.0%)	0–7 years: 96 (39.3%) 8–14 years: 96 (39.3%) 14+ years: 52 (21.3%)	<**0.001**
Stroke	1511	65 (6.3%)	35 (7.3%)	0.445
Hypertension	1501	327 (31.8%)	149 (31.6%)	0.965
Diabetes	1584	84 (7.8%)	38 (7.5%)	0.856
Angina/myocardial infarction	1605	185 (17.0%)	110 (21.7%)	**0.024**
APOE ε4	2204	543 (35.4%)	213 (31.8%)	0.108
Cohabiting	2288	599 (37.6%)	542 (78.2%)	<**0.001**
Alcohol (range 1–4)	2289	1.5 (1.6)	1.6 (1.6)	0.122
Physically active (yes/no)	2281	939 (59.1%)	495 (71.6%)	<**0.001**
Smoking	2249	372 (23.7%)	412 (60.6%)	<**0.001**
Hopelessness (range 0–6)	1622	1.3 (1.4)	1.2 (1.3)	0.096
Sleep disturbances (range 0–2)	1572	0.53 (0.8)	0.43 (0.7)	<**0.001**

Notes: To obtain *P*-values, logistic regressions were carried out for continuous variables, and chi-square for categorical variables.
Values are means (SD) for continuous variables and numbers (%) for continuous variables. Bold *P*-values indicate $P < 0.05$.
Abbreviations: *APOE*, apolipoprotein E; CAIDE, The Cardiovascular Risk Factors, Aging and Dementia study; H70, The Gothenburg H70 Birth Cohort Studies; KP, Kungsholmen Project; SD, standard deviation.

TABLE 2 Sociodemographic and clinical characteristics of participants in the CAIDE study for long follow-up analyses

Long follow-up (only CAIDE)	N	Women (n = 941)	Men (n = 569)	*P*-value
Dementia cases	1510	174 (18.5%)	98 (17.2%)	0.534
Baseline age (range 39–64)	1510	50.5 (6.1)	49.9 (5.8)	**0.038**
Age > 80 years at first re-examination	1414	8 (0.9%)	2 (0.4%)	0.238
Age > 80 years at second re-examination	896	199 (34.2%)	90 (28.7%)	0.091
Follow-up from baseline to first re-examination	1502	20.9 (5.0)	21.0 (4.8)	0.611
Follow-up from baseline to second re-examination	888	28.9 (5.1)	29.1 (4.8)	0.602
Education (range 0–23 years)	1477	8.4 (3.2)	8.8 (3.7)	**0.042**
Stroke	1510	114 (12.1%)	96 (16.9%)	**0.010**
Hypertension	608	250 (64.1)	146 (67.0)	0.476
Diabetes	1510	84 (8.9%)	64 (11.3%)	0.142
Angina/myocardial infarction	1510	44 (4.7%)	34 (6.0%)	0.269
APOE ε4	1379	289 (33.9%)	201 (38.2%)	0.103
Cohabiting	1509	684 (72.7%)	521 (91.7%)	**<0.001**
Alcohol (range 1–9)	1085	63 (9.4%)	150 (36.4%)	**<0.001**
Physical activity (range 0–5)	1468	342 (37.8%)	253 (45.0%)	**0.006**
Smoking	1509	218 (23.2%)	433 (76.2%)	**<0.001**
Hopelessness	1455	3.2 (1.8)	2.9 (1.8)	**0.002**
Insomnia (range 1–3)	1363	1.5 (0.7)	1.4 (0.6)	**<0.001**

Notes: To obtain *P*-values, logistic regressions were carried out for continuous variables, and chi-square for categorical variables.
Values are means (SD) for continuous variables and numbers (%) for continuous variables. Bold *P*-values indicate $P < 0.05$.
Abbreviations: *APOE*, apolipoprotein E; CAIDE, The Cardiovascular Risk Factors, Aging and Dementia study; SD, standard deviation.

2.4 | Multidomain lifestyle intervention trial

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is a 2-year population-based multidomain randomized controlled trial. The trial was carried out in six different sites in Finland, and enrolled participants from the general population who had an increased risk for dementia according to the CAIDE Dementia Risk Score (n = 1260, age range: 60–79). The trial protocol, recruitment process, and primary findings have been previously described.[34] FINGER was approved by the coordinating ethics committee of the Hospital District of Helsinki and Uusimaa (ClinicalTrials.gov Identifier: NCT01041989).

2.5 | Intervention

The control group received regular health advice according to established guidelines. The multidomain lifestyle intervention included four components: The *nutritional component*, carried out by study nutritionists, included both individual and group sessions. The *exercise training program* was led by study physiotherapists at the gym, with both group and individual sessions. Participants had tailored programs for progressive muscle strength training, aerobic exercise, and postural balance exercises. *Cognitive training* was led by a psychologist and included group and individual sessions. Individual sessions involved computer-based training at home or at the study site. *Management of metabolic and vascular risk factors* followed national evidence-based guidelines. Participants met the study nurse and physician for medical assessments and measurements of vital signs and anthropomorphic measures, and received lifestyle recommendations. (For a detailed description of the intervention please see Ngandu et al.[34] and Kivipelto et al.[35]).

2.6 | Outcomes

Participants performed a standard cognitive assessment with an extended version of the Neuropsychological Test Battery (NTB) at baseline, 12-, and 24-month visits. Participants who dropped out during the study were invited to a final visit at 24 months for outcome evaluation. The primary FINGER outcome was cognitive change measured by NTB total score, a composite score based on results from 14 tests (calculated as Z scores standardized to the baseline mean and standard deviation [SD], with higher scores suggesting better performance). Secondary cognitive outcomes included

NTB domain Z scores for memory, processing speed, and executive functioning.[34]

2.7 | Statistical analyses

Analyses were performed using Stata 14.0 (Stata Corp). For baseline characteristics, we used $\chi 2$ tests for categorical variables (data reported as percentages) and binary logistic regressions with sex as outcome for continuous variables (data reported as means [SD]). We included two sets of analyses: short-term follow-up, for which baseline was conducted in old age, and follow-up duration was ≈3 to 10 years; and long-term follow-up, for which baseline was conducted in mid-life, and follow-up duration was ≈20 to 30 years.

The significance level for all analyses was set at $P < 0.05$. For the population-based cohort studies hazard regressions with Gompertz-distributed baseline intensity were used in the analyses with long follow-up to investigate whether there are sex differences in the development of dementia and interactions between sex and risk factors, and their association with dementia. Hazard regressions with Gompertz-distributed baseline intensity is preferred to Cox regressions as they are less sensitive to misspecifications of time. In the analyses with short follow-up we include several data sets with different number of follow-ups with different timings. This makes the risk for erroneous specification of time even larger. Because of this, logistic regressions with data in long format were used. We have applied models with right censoring both for logistic and hazard regressions—meaning that persons are considered at risk until they are diagnosed with dementia. Applying logistic regressions with right censoring, controlling for time from baseline, to data with long format corresponds to hazard regressions with discrete time.[36,37]

For both short and long follow-up associations, we analyzed the risk for dementia in a similar way. All analyses are controlled for age and follow-up time (and study site for short follow-up). The results are based on several models, initially: (1) sex differences; (2) sex differences in age ≦ 80; and (3) sex differences in age > 80+ (presented at the top of the tables). For each of the risk factors separately we ran two models: (1) including sex, the risk factors and the interaction between the risk factor and sex—with WOMEN as the reference category for sex; (2) including sex, the risk factors and the interaction between the risk factor and sex—with MEN as the reference category for sex; (3) the interaction terms show the difference between men and women with WOMEN as the reference category. An odds ratio (OR) > 1.0 indicates that the association between risk factors and dementia risk is higher among men than among women. *P*-value for the interaction shows if the association differs between women and men.

For the multidomain lifestyle intervention trial, mixed-model repeated-measures and three-way interaction analyses were used to assess whether the intervention effects on the primary and secondary cognitive outcomes varied between women and men.

Linear mixed models for repeated measures were used to assess whether sex influenced the intervention effects on the primary and secondary cognitive outcomes, that is, the 2-year change in cognitive performance measured with the NTB. The models included group allocation (intervention or control), time, sex, and all interaction terms as predictors. The study site was entered in the model as a covariate. Coefficients for the three-way interaction terms (group x time x sex) and the corresponding *P*-values are shown as the main results. Estimates for the change in cognition in the intervention and control groups within each subgroup (men and women) as well as the difference of these estimates were obtained from the mixed models with the linear combinations of estimators (lincom) post-estimation command in STATA.

3 | RESULTS

3.1 | Population-based cohort studies

3.1.1 | Sex differences in sociodemographic and clinical characteristics

Characteristics for multi-center data, CAIDE, H70, KP used for short-follow-up analyses

At the late-life assessments (N = 2289), mean age at baseline: women: 76.0 (SD = 6.9), men: 73.6 (6.0); average follow-up time: women = 6.0 (2.5) years, men 6.5 (2.4) years; total dementia cases = 466; and number lost to follow-up: 799 (26%). Women had a higher prevalence of dementia, were older, had a higher proportion of participants age > 80, shorter follow-up time, lower levels of education, lower prevalence of angina/myocardial infarction, were less likely to be cohabiting, had less consumption of alcohol, were less likely to be physically active, were less likely to be smokers, and had more sleep disturbances. No significant differences were found for other factors (see Table 1).

Characteristics for CAIDE data (N = 1510), used for long-follow-up analyses

Average time to first follow-up: women = 20.9 (SD = 5.0) years, men 21.0 (4.8) years; average time to second follow-up: women = 28.9 (5.1) years, men 29.1 (4.8) years.

At the mid-life assessment women were older (mean age at baseline: women = 50.5 [SD = 6.1]; men = 49.9 [SD = 5.8]), had lower levels of education, lower prevalence of stroke, were less likely to be cohabiting, had lower alcohol consumption, had lower levels of physical activity, were less likely to be smokers, had higher levels of hopelessness, and had more insomnia symptoms. No significant differences were found for other factors (see Table 2).

Sex differences in the development of dementia

Analyses with short follow-up (baseline in late-life: Multi-center data [CAIDE, H70, KP]). When including all age groups women and men did not significantly differ in the risk for dementia (OR women vs. men: 1.18, $P = 0.189$, 95% confidence interval [CI]: 0.92–1.51), when adjusting for age, follow-up time, and study. Women showed a higher risk of developing dementia after the age of 80 years (OR: 1.37,

TABLE 3 Associations between risk factors and dementia for women and men, and the interaction between sex and risk factors in relation to dementia

Analyses with **short follow-up (CAIDE, H70, and KP data combined).**						
Overall analyses women versus men: OR: 1.18, $P = 0.189$, CI: 0.92–1.51						
Women versus men ≤ 80: OR: 0.93, $P = 0.775$, CI: 0.56–1.51						
Women versus men > 80: **OR: 1.37, $P = 0.030$, CI: 1.03–1.83**						
	Women[a]		**Men**[b]		**Difference**[c]	
Risk factors	**OR**	**CI**	**OR**	**CI**	**OR**	**CI**
Education	**0.93**	**0.87–0.99**	0.99	0.92–1.07	1.07	0.96–1.18
Stroke	1.06	0.55–2.04	**4.24**	**1.70–10.60**	**3.99**	**1.30–12.31**
Hypertension	1.02	0.71–1.47	1.89	0.94–3.80	1.85	0.84–4.05
Diabetes	1.28	0.68–2.40	0.80	0.18–3.49	0.63	0.13–3.10
Angina/myocardial infarction	0.99	0.65–1.50	1.15	0.54–2.45	1.16	0.49–2.78
Total cardiovascular risk factors	1.13	0.81–1.57	1.35	0.70–2.60	1.19	0.57–2.49
APOE ε4	**1.40**	**1.10–1.47**	**2.05**	**1.29–3.25**	1.47	0.87–2.46
Cohabiting	**0.67**	**0.51–0.89**	**0.62**	**0.39–0.98**	0.92	0.54–0.89
Alcohol	1.10	1.00–1.21	0.93	0.77–1.13	0.85	0.68–1.05
Physical activity	**0.64**	**0.49–0.83**	0.91	0.58–1.43	1.43	0.87–2.35
Smoking	0.84	0.63–1.13	1.05	0.67–1.65	1.25	0.73–2.13
Hopelessness	**1.34**	**1.14–1.56**	**1.53**	**1.22–1.93**	1.15	0.90–1.46
Sleep disturbances	1.21	0.99–1.49	**1.51**	**1.04–2.20**	1.25	0.82–1.90

Notes: Logistic regressions on data in long format. Analyses are controlled for age, follow-up time, and study.
A total cardiovascular risk factors variable was computed considering the low numbers for some of the cardiovascular risk factors.
For each of the risk factors separately, presented as the main part of the table, we ran two models.
[a]Including sex, the risk factors and the interaction between the risk factor and sex—with MEN as the reference category for sex.
[b]Including sex, the risk factors and the interaction between the risk factor and sex—with WOMEN as the reference category for sex.
[c]The interaction terms show the difference between men and women with WOMEN as the reference category. An odds ratio > 1.0 indicates that the association between risk factors and dementia risk is higher among men than among women. *P*-value for the interaction shows if the association differs between women and men.
Bold values indicate $P < 0.05$.
Abbreviations: *APOE*, apolipoprotein E; CAIDE, The Cardiovascular Risk Factors, Aging and Dementia study; CI, confidence interval; H70, The Gothenburg H70 Birth Cohort Studies; KP, Kungsholmen Project; OR, odds ratio; SD, standard deviation.

$P = 0.030$, 95% CI: 1.03–1.83), whereas no sex difference was observed for the development of dementia before the age of 80 (OR: 0.93, $P = 0.775$,95% CI: 0.56–1.51; see Table 3).

Analyses with long follow-up (baseline in mid-life ([CAIDE data]). Results showed that women and men did not significantly differ in the risk for dementia (hazard ratio [HR] women vs. men: 1.02, $P = 0.853$, 95% CI: 0.80–1.31), when adjusting for age and follow-up time. No sex differences were detected when examining the risk for dementia diagnosis before or after the age of 80 years (≤80 years: OR: 0.89, $P = 0.424$, 95% CI: 0.66–1.19; > 80 years: OR: 1.23, $P = 0.413$, 95% CI: 0.75–1.99; see Table 4).

Interactions between sex and risk factors, and their association with dementia

Analyses with short follow-up (baseline in late-life: multi-center data [CAIDE, H70, KP]). The analyses showed one significant interaction between sex and the dementia risk factors assessed. There was no association between stroke and dementia risk among women, but a strong and significant association among men (Table 3). The interaction between sex and stroke shows that the OR for the association between stroke and dementia is 3.99 times stronger among men than among women (4.24/1.06 = 3.99; $P = 0.016$).

Sex-specific analyses showed that among women, lower education, *APOE ε4* allele, not cohabiting, physical inactivity, and hopelessness were significantly associated with an increased risk for dementia. Among men, history of stroke, *APOE ε4* allele, not cohabiting, more severe sleep disturbances, and hopelessness were significantly associated with an increased risk for dementia.

Analyses with long follow-up (baseline in mid-life [CAIDE data]). Interactions between sex and each of the risk factors were used to study if associations between risk factors and dementia differed between women and men. A significant interaction was found between sex and physical inactivity, meaning that the associations between physical inactivity and dementia differed significantly between women and men

TABLE 4 Associations between risk factors and dementia for women and men, and the interaction between sex and risk factors in relation to dementia

Analyses with **long follow-up (CAIDE data).**						
Overall analyses women versus men: HR: 1.02, $P = 0.853$, CI: 0.80–1.31						
Women versus men ≤ 80: HR: 0.89, $P = 0.424$, CI: 0.66–1.19						
Women versus men > 80: HR: 1.23, $P = 0.413$, CI: 0.75–1.99						
	Women[a]		**Men**[b]		**Difference**[c]	
Risk factors	**HR**	**CI**	**HR**	**CI**	**HR**	**CI**
Education	**0.91**	**0.86–0.96**	0.96	0.91–1.02	1.06	0.98–1.15
Stroke	**2.45**	**1.72–3.47**	1.51	0.94–2.43	0.62	0.34–1.12
Hypertension	**1.01**	**1.01– 1.02**	1.01	0.99–1.02	0.99	0.98–1.00
Diabetes	**1.65**	**1.07–2.53**	0.92	0.48–1.78	0.56	0.26–1.23
Angina / myocardial infarction	1.33	0.93–1.92	1.36	0.84–2.21	1.02	0.56–1.87
APOE ε4	**1.93**	**1.41–2.63**	**2.63**	**1.71–4.05**	1.37	0.80–2.32
Cohabiting	**0.70**	**0.50–0.97**	0.59	0.32–1.11	0.85	0.42–1.72
Alcohol	1.54	0.90–2.63	1.21	0.75–1.94	0.79	0.38–1.61
Physical activity	**0.61**	**0.40–0.93**	1.10	0.80–1.50	**1.81**	**1.06–3.07**
Present smoker	0.84	0.59–1.20	0.99	0.61–1.60	1.18	0.64–2.15
Hopelessness	1.07	0.98–1.16	1.06	0.95–1.18	1.00	0.86–1.13
Insomnia	**1.38**	**1.10–1.73**	1.12	0.79–1.58	0.81	0.54–1.23

Notes: Hazard regressions with Gompertz distributed baseline intensity. Analyses are controlled for age and follow-up time.
The results in Table 4 are based on several models: (1) sex differences; (2) sex differences in age ≦ 80; and (3) sex differences in age > 80+ presented at the top of the table.
For each of the risk factors separately, presented as the main part of the table, we ran two models:
[a]Including sex, the risk factor and the interaction between the risk factor and sex—with MEN as the reference category for sex.
[b]Including sex, the risk factor and the interaction between the risk factor and sex—with WOMEN as the reference category for sex.
[c]The interaction terms show the difference between men and women with WOMEN as the reference category. A hazard ratio > 1.0 indicates that the association between risk factors and dementia risk is higher among men than among women. *P*-value for the interaction shows if the association differs between women and men.
Bold values indicate $P < 0.05$.
Abbreviations: *APOE*, apolipoprotein E; CAIDE, The Cardiovascular Risk Factors, Aging and Dementia study; CI, confidence interval; HR, hazard ratio; SD, standard deviation.

(Table 4). Women have a significantly higher risk for dementia than men among participants who were physically inactive (not presented in a table).

Sex-specific analyses showed that among women, lower education, history of stroke, hypertension and diabetes, *APOE ε4* allele, physical inactivity, not cohabiting, and more severe insomnia were significantly associated with an increased risk for dementia. Among men, the *APOE ε4* allele was significantly associated with an increased risk for dementia.

3.2 | Multidomain lifestyle intervention trial

3.2.1 | Sex differences in baseline characteristics among FINGER participants

Baseline characteristics of men and women in the FINGER trial (intention-to-treat population, all randomized participants) are shown in Table 5. There were several differences between women and men at baseline. Compared to men, women were older, had lower education, and were less frequently married or cohabiting. Approximately one third of both men and women were *APOE ε4* carriers. In terms of vascular factors, women had lower diastolic blood pressure, higher body mass index, total cholesterol, high density lipoprotein cholesterol, and low density lipoprotein cholesterol, but lower fasting plasma glucose concentration than men. Moreover, women had lower prevalence of previous myocardial infarction. Although several lifestyle-related risk factors were present among both sexes, men seemed to have an unhealthier lifestyle than women. Despite no significant difference in smoking and physical activity, men consumed alcohol more frequently, and their fish and vegetable intake was lower. In addition to vascular and lifestyle-related risk factors, men and women differed in their cognitive performance: women had higher NTB total score and domain-specific scores for memory and processing speed, whereas men performed better in tasks related to executive functioning.

TABLE 5 Baseline characteristics of FINGER participants

Baseline characteristics	N	Women (n = 588)	Men (n = 672)	*P*-value for difference
Demographic characteristics				
Age at baseline, years (range 59.8–80.0)	1260	69.7 (4.7)	69.1 (4.7)	**0.039**
Education, years (range 0–30)	1258	9.6 (3.2)	10.3 (3.6)	**0.002**
Married or cohabiting	1259	356/587 (60.7)	579/672 (86.2)	<**0.001**
APOE ε4 carrier	1175	189/549 (34.4)	200/626 (32.0)	0.368
Vascular factors				
Systolic blood pressure, mmHg (range 93.5–215.0)	1249	139.8 (15.7)	140.3 (16.6)	0.599
Diastolic blood pressure, mmHg (range 41.5–115.0)	1249	79.0 (9.4)	81.5 (9.4)	<**0.001**
Body mass index, kg/m^2 (range 15.2–58.7)	1249	28.8 (5.3)	27.7 (4.0)	<**0.001**
Serum total cholesterol, mmol/l (range 2.5–8.8)	1255	5.4 (1.0)	4.9 (1.0)	<**0.001**
HDL-C, mmol/l (range 0.6–3.2)	1255	1.6 (0.4)	1.3 (0.3)	<**0.001**
LDL-C, mmol/l (range 0.9–6.5)	1255	3.2 (0.9)	3.0 (0.9)	<**0.001**
Fasting plasma glucose, mmol/l (range 4.4–16.9)	1257	5.9 (0.8)	6.2 (0.9)	<**0.001**
2 hours oral glucose tolerance test, mmol/l (range 1.9–19.9)	1085	7.1 (2.2)	7.0 (2.2)	0.271
Lifestyle factors				
Physical activity two or more times per week	1247	422/578 (73.0)	461/669 (68.9)	0.112
Current smokers	1255	46/585 (7.9)	68/670 (10.2)	0.160
Alcohol drinking at least once per week	1252	153/582 (26.3)	403/670 (60.2)	<**0.001**
Fish intake at least twice per week	1253	328/581 (56.5)	328/672 (48.8)	**0.007**
Daily intake of vegetables	1257	400/587 (68.1)	376/670 (56.1)	<**0.001**
Self-reported medical disorders				
Hypertension	1246	392/580 (67.6)	429/666 (64.4)	0.239
Hypercholesterolemia	1250	403/584 (69.0)	437/666 (65.6)	0.203
Diabetes	1253	68/585 (11.6)	97/668 (14.5)	0.130
History of myocardial infarction	1254	14/586 (2.4)	50/668 (7.5)	<**0.001**
History of stroke	1251	29/585 (5.0)	39/666 (5.9)	0.484
Cognition				
NTB total score (range −1.88–1.54)	1259	0.07 (0.56)	−0.07 (0.59)	<**0.001**
Executive functioning (range −2.12–2.13)	1258	−0.07 (0.65)	0.04 (0.70)	**0.003**
Memory (range −1.78–2.13)	1259	0.17 (0.67)	−0.15 (0.65)	<**0.001**
Processing speed (range −3.18–2.43)	1259	0.09 (0.81)	−0.08 (0.82)	<**0.001**
MMSE (range 20–30)	1257	26.7 (2.1)	26.8 (1.9)	0.248

Data are n (%) or mean (SD). Baseline characteristics are shown for the intention-to-treat (ITT) population (all randomized participants). NTB total score and scores for executive functioning, processing speed, and memory are mean values of Z scores of the cognitive tests in each domain, and higher scores indicate better performance. $\chi 2$ tests and *t* tests were performed for categorical and continuous variables, respectively. *P*-values in bold indicate statistically significant difference between men and women ($P < 0.05$).

Abbreviations: *APOE*, apolipoprotein E; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; NTB, Neuropsychological Test Battery.

3.2.2 | Influence of sex on intervention effects on the primary and secondary cognitive outcomes

Mixed-model repeated-measures analyses including interactions between sex and intervention versus control were used to investigate whether the intervention effects on the primary and secondary cognitive outcomes varied between women and men (group x time x sex interactions). Data are based on all participants with at least one post-baseline measurement (modified intention to treat population): N = 591 for the intervention group (267 women and 324 men) and N = 599 for the control group (284 women and 315 men). The interaction was non-significant ($P > 0.05$) for the primary outcome (NTB) and

TABLE 6 Influence of sex on intervention effects on the primary and secondary cognitive outcomes

Cognitive outcomes		Estimate (β-coefficients) for difference between intervention and control group per year (95% CI)	*P*-value for interaction
NTB total score	Men	0.022 (−0.005–0.050)	0.98
	Women	0.022 (−0.007–0.051)	
Executive functioning	Men	**0.049 (0.015–0.084)**	0.07
	Women	0.002 (−0.035–0.039)	
Processing speed	Men	0.011 (−0.026–0.048)	0.14
	Women	**0.052 (0.012–0.092)**	
Memory	Men	0.009 (−0.035–0.054)	0.68
	Women	0.023 (−0.025–0.071)	

Cognitive outcomes		Difference between intervention and control group per year		*P*-value for interaction
		Estimate (95% CI)	*P*-value	
NTB total score	Men	0.022 (−0.005–0.050)	0.104	0.977
	Women	0.022 (−0.007–0.051)	0.141	
Executive functioning	Men	**0.049 (0.015–0.084)**	0.005	0.067
	Women	0.002 (−0.035–0.039)	0.915	
Processing speed	Men	0.011 (−0.026–0.048)	0.568	0.136
	Women	**0.052 (0.012–0.092)**	0.010	
Memory	Men	0.009 (−0.035–0.054)	0.676	0.679
	Women	0.023 (−0.025–0.071)	0.339	

The *P*-values for interaction show whether the intervention effects differ between women and men (non-significant *P*-values indicate no significant effect modification by sex). Bold *P*-values indicate $P < 0.05$.
Abbreviations: CI, confidence interval; NTB, Neuropsychological Test Battery.

the secondary cognitive outcomes (executive functioning, processing speed, and memory), indicating that sex does not significantly modify the intervention effects on cognition (Table 6). A positive value of the estimate for the difference between intervention and control groups indicates that the effect is in favor of the intervention group (Figure 1).

3.2.3 | Experiences and feedback from the FINGER intervention

Detailed feedback regarding the FINGER intervention was gathered using structured questionnaires from all participants who received the multidomain lifestyle intervention and attended the 2-year follow-up visit (n = 555). (These results are not presented in a table or figure.) Questions focused on self-reported adherence, common experiences, and benefits and usefulness of the intervention. The results showed that participants perceived the intensive 2-year FINGER multidomain lifestyle intervention as useful, and most participants intended to continue the healthy lifestyle changes after the intervention. There were no sex differences in self-reported adherence to any intervention domains. The majority of both women and men perceived that it was pleasant to meet other participants in the intervention sessions. In total, 57% of women and 50% of men reported that meeting other participants motivated them to participate (Pearson chi square $P = 0.313$). There were no sex differences in perceived usefulness of nutritional counseling ($P = 0.135$) or cognitive training ($P = 0.381$). Also, 95% of women and 92% of men ($P = 0.210$) reported that they received sufficient information to independently continue physical activity training after the intervention.

Participants in the FINGER trial were not actively told to which group they belong. Almost half of the participants in the intervention group did not consider themselves taking part in an intensive intervention. A total of 44% (n = 236) of participants in the intervention group believed they belonged to the regular health advice group (39% of women, 49% of men, Pearson chi square $P = 0.008$).

4 | DISCUSSION

This study showed that while women and men did not differ in their risk for developing dementia across all age groups, women had a higher risk after the age of 80 years. This indeed is an important group that comprises ≈70% of all dementias. Associations between the investigated risk factors and dementia did not significantly differ between women and men. However, sex-specific analyses suggested that different vascular, lifestyle, and psychosocial risk factors may be important

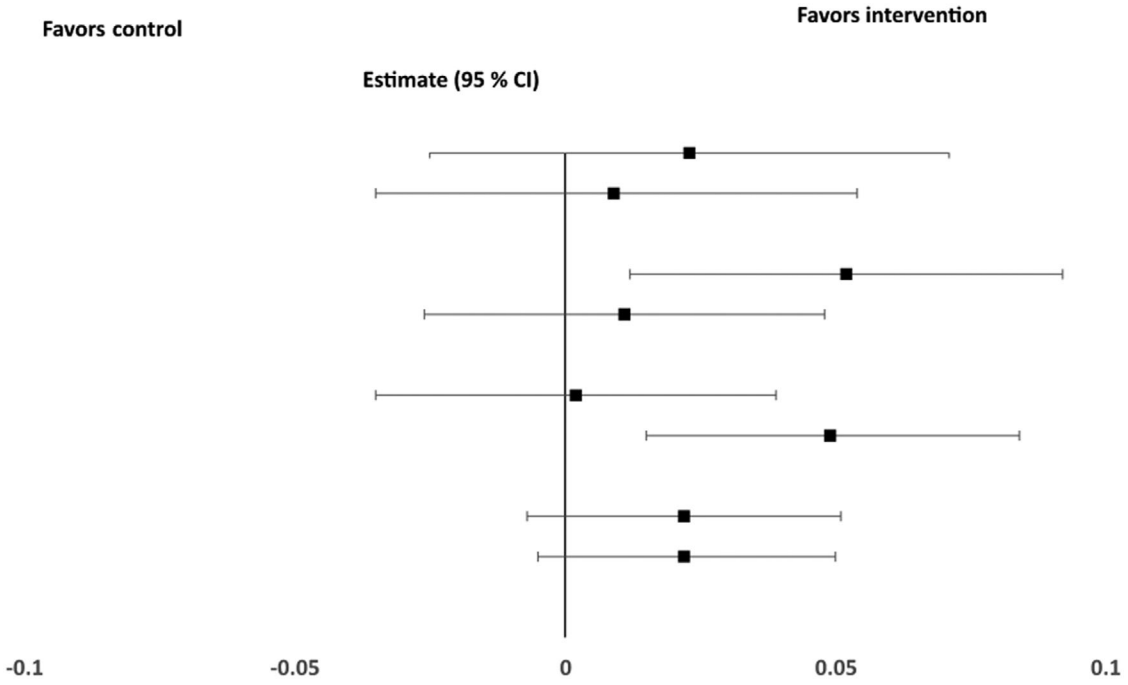

FIGURE 1 Difference between intervention and control group regarding intervention effects. A positive value of the estimate for the difference between intervention and control groups indicates that the effect is in favor of the intervention group. Bars represent 95% confidence intervals (CIs) of the estimates. Data are based on all FINGER participants with at least one post-baseline measurement (modified intention to treat population). N = 591 for the intervention group (324 men and 267 women) and N = 599 for the control group (315 men and 284 women). Analyses are adjusted for study site

for women and men in mid- and late-life. Women and men participating in the FINGER trial had different risk profiles but the positive effect of the multi-domain lifestyle intervention was detected among both women and men.

When assessing the development of dementia at any age, the results showed that women and men did not significantly differ in the risk for dementia (regardless of whether baseline assessments took place in mid-life or late-life), which supports previous findings (for reviews see Li and Singh[9] and Mielke et al.[27]). The higher dementia risk for women after the age of 80 years, which was observed when pooling the three large cohort studies, is also consistent with previous findings.[3,5–7] These results may be due to a selective survival of men who live into old age, considering the higher prevalence and mortality of men from cardiovascular conditions in mid-life.[8,11] We also cannot rule out that longer life expectancy among women plays a role, and higher dementia incidence among women is observed among the oldest old. That these results were not detected in the CAIDE sample only may be due to insufficient power, but these findings were also observed when pooling the three large cohort studies.

Sex-specific analyses showed that among women, lower education, history of stroke (assessed in mid-life), *APOE* ε4, not cohabiting, physical inactivity, hopelessness (assessed in late-life), and more severe insomnia (assessed in mid-life), were all associated with an increased risk for dementia. Among men, history of stroke (assessed in late-life), *APOE* ε4, not cohabiting (assessed in late-life), hopelessness (assessed in late-life), and more severe insomnia (assessed in late-life) were all associated with an increased risk for dementia.

As the *APOE* ε4 allele is one of the strongly established risk factors for dementia, our results support previous findings, as we show that it was significantly associated with dementia risk among both women and men. Previous findings showed that the *APOE* ε4 allele increases one's lifetime risk of developing AD from 14% in women and 11% in men to 30% and 23% (for those carrying one copy of the allele, "heterozygotes"), to 60% and 50%, respectively (among those carrying two copies of the allele, "homozygotes").[38] Our sample was not sufficiently powered to assess differences between hetero- and homozygotes, but this is important for future research to confirm.

That lower education levels were only associated with dementia risk among women supports previous research suggesting that men tend to have greater cognitive reserve, possibly due to higher educational attainment and more mentally stimulating occupations (for reviews see Mielke et al.[27] and Rocca et al.[39]). In more recent years, women have had an increase in educational and occupational attainment (e.g., in Western/Northern Europe and North America), and this may have contributed to the recent reduction in age-specific dementia incidence and prevalence.[40,41] A recent study confirmed this notion in a population-based sample of 85-year-olds, showing that the decrease in dementia (between 1986–1987 and 2008–2010) was primarily attributed to higher educational attainment.[42] This also highlights the importance of taking into account cohort effects when investigating such factors that change across time, as previously shown.[43,44] The importance of

hopelessness in late-life among women and men supports our previous findings, which showed that hopelessness and depression are important risk factors.[45,46] More generally, these findings emphasize the role of psychosocial factors and affective disorders in late-life as marked dementia risk factors.[47]

Our sex-specific analyses showed among women, physical inactivity was an important risk factor in mid- and late-life. To date, findings in the literature are mixed on whether physical inactivity is a stronger risk factor among women or men.[48–51] These discrepancies may be due to the different time periods when physical activity was measured, the type of physical activity, and the timing of cognitive measures. In one study, exercise in teenage years, at ages 30, 50, and late-life were each associated with a reduced risk for cognitive impairment,[52] highlighting the importance of a life-course approach. Moreover, the observed significant association of stroke history with the risk for dementia among men underscores the role of vascular risk factors and comorbidities. These results also add to the emerging literature on the role of sleep disturbances as important dementia risk factors.[32] The current results suggest that while sleep disturbances in late-life are associated with an increased dementia risk, women may be more vulnerable to midlife sleep disturbances (insomnia).

Findings from the FINGER lifestyle intervention showed that sex did not modify the intervention effects on cognition. There were also no clear sex differences in participants' adherence to the intervention domains, or in the subjective experiences of participating in the trial. Both sexes considered their participation positive, the information they received as useful (regarding the different intervention domains), and that they received sufficient information to sustain the lifestyle changes. The FINGER extended follow-ups (5 and 7 years) will demonstrate whether there are sex differences in the long-term adherence and incidence of cognitive impairment after the 2-year lifestyle intervention.

The fact that the positive benefits of the FINGER intervention were not significantly different between women and men is promising, and suggests that the intervention is well tailored and applicable for both sexes. It was also reassuring to observe that both sexes had positive experiences and feedback. The current emphasis is on using a precision medicine approach when designing preventive interventions.[53] The evidence from the FINGER trial suggests that while it is important to take sex differences into account, when designing future similar interventions, more efforts can be invested in adaptations to different cultures; age groups; other vascular, lifestyle, psychosocial, and demographic risk factors; as well as family history of dementia. In contrast, stratification by sex has been suggested for some drug trials, considering the potential physiological interactions with sex hormones that may impact safety and tolerability of drugs,[54] in addition to potential sex differences in pharmacokinetics and pharmacodynamics. In general, there still remains a need for more tailored interventions to maximize the adherence and efficacy of various interventions.

In addition to the current findings, the role of sex hormones and hormone replacement therapy (HRT) may have played a more important role in the analyses among those below the age of 80, compared to those above the age of 80, and this should be considered when interpreting the findings. The evidence on HRT is still mixed and warrants further investigation (for reviews see Mielke et al.[27] and Rocca et al.[39,55]). Observational studies have confirmed the neuroprotective effects of estrogen, but evidence from clinical trials using HRT has not necessarily supported this notion. The inconsistencies may be due to the HRT "window of opportunity"; HRT may be beneficial only if started soon (within 5 years) after menopause or surgical removal of the ovaries,[56] and our findings from the CAIDE study supported this hypothesis.[57] There have also been important demographic and health differences across study designs; HRT users were more educated and had higher socioeconomic status and better overall health.

This study has several strengths, including several large well-characterized observational studies, and analyzing data from both mid-life and late-life, with long follow-up durations and standardized dementia diagnoses, as well as using register-based diagnoses to reduce the risk of survival and participation bias in the long follow-up analyses. Also, the analytic model adopted considers differences in hazard assessment according to age, and therefore, the findings regarding risk among women above the age of 80 years are robust. The FINGER trial is the first large multidomain intervention showing that lifestyle intervention may reduce cognitive decline. The current results confirm that these beneficial intervention effects can be observed among both women and men, regardless of other baseline characteristics. Additionally, for the first time, we report sex differences in baseline characteristics of the FINGER sample, interactions between sex and the secondary outcomes on cognitive domains, and we investigate sex differences in participants' experiences and feedback.

There are a few limitations worth mentioning. First, we did not have sufficient power to investigate dementia subtypes, and considering that AD and other types of dementia may have different risk factors, the results need to be interpreted with caution. Second, we do not have information on time to death (a competing risk). Third, loss at follow-up and selection bias is always a potential limitation in long-term cohorts and when studying older adults. Because dementia and mortality partially have the same risk factors, we are likely to underestimate the associations between risk factors and dementia. Fourth, due to harmonizing the data across the observational studies, we could not investigate the different risk factors in more detail. Also, while we investigate the role of sleep disturbances, sleep disorders may also be important to consider. Although we had large sample sizes (for both the population-based studies and the lifestyle interventions), larger numbers and more statistical power may have been needed to detect interaction effects, as well as differences in dementia risk among women after the age of 80 in the CAIDE study with long follow-up. Register-based dementia diagnoses rely on ICD codes, and this approach may miss a proportion of dementia cases. The large number of comparisons also may have increased the probability of having chance findings. Finally, the first follow-up in CAIDE was based on individuals that had survived until 1998, and we have no information about those who had died between both time points, and this may have led to selective survival. Attrition between the first and second follow-up could also not be accounted for, possibly contributing as an additional source of selection.

In conclusion, this study shows that the risk of dementia does not differ between the sexes across all age groups, but after the age of 80 the risk is higher among women. Different risk factors in mid-life

and late-life may be important for dementia risk among women and men. However, there were no clear differences between the sexes in the benefits of a lifestyle intervention—in terms of improved cognitive performance and participation experiences—between the sexes. It will be important for future research to investigate sex differences in large, sufficiently powered and well-characterized datasets, both from observational and interventional studies, considering interactions among lifestyle factors, sex hormones, and cognitive reserve using multiple indicators within a life-course perspective. This may open new avenues for interventions and more tailored intervention approaches.

ACKNOWLEDGMENTS

The authors would like to thank the participants in all four studies for their time and valuable contributions. The funding sources had no role in the analyses, interpretations, and decision to publish the paper. Shireen Sindi receives research support from the Swedish Research Council, Alzheimerfonden, Demensförbundet, Karolinska Institute Foundation and Funds (KI Stiftelser och Fonder), Loo and Hans Osterman Foundation for Medical Research and Erik Rönnbergs Stipend – Riksbankens Jubileumsfond. Hui-Xin Wang receives funding from the Swedish Research Council (grant number 2018-02998), the Swedish Research Council for Health, Working Life and Welfare (grant numbers 2019-01120 and 2020-00313). Miia Kivipelto receives research support from the Academy of Finland, Finnish Social Insurance Institution, Finnish Ministry of Education and Culture, Juho Vainio Foundation (Finland), EVO/VTR grants of University Hospitals of Kuopio, Oulu and Turku, Seinäjoki Central hospital and Oulu City Hospital for FINGER trial, the Swedish Research Council for Joint Programme – Neurodegenerative Disease Research (MIND-AD and EURO-FINGERS), Alzheimerfonden (Sweden), Swedish Research Council (Research Environment Grant Ageing and Health), Center for Innovative Medicine (CIMED) at Karolinska Institutet, Region Stockholm (ALF, NSV), AXA Research Fund, Knut and Alice Wallenberg Foundation (Sweden), Stiftelsen Stockholms sjukhem (Sweden), Konung Gustaf V:s och Drottning Victorias Frimurarstiftelse (Sweden), and Swedish Research Council for Health, Working Life and Welfare (FORTE). Laura Fratiglioni is receives grants from Swedish Research Council (Research Environment Grant Ageing and Health), and Swedish Research Council for Health, Working Life and Welfare (FORTE). Ingmar Skoog received grants from the Swedish Research Council, the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (ALF 716681), Swedish Research Council for Health, Working Life and Wellfare, Alzheimerfonden (Sweden), Hjärnfonden, Swedish Brain Foundation, Konung Gustaf V:s och Drottning Victorias Frimurarestiftelse, The Alzheimer's Association (USA).

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

REFERENCES

1. 2020 Alzheimer's disease facts and figures. *Alzheimer's Dement*. 2020;16:391-460.
2. De Deyn PP, Goeman J, Vervaet A, Dourcy-Belle-Rose B, Van Dam D, Geerts E. Prevalence and incidence of dementia among 75-80-year-old community-dwelling elderly in different districts of Antwerp, Belgium: the Antwerp Cognition (ANCOG) Study. *Clin Neurol Neurosurg*. 2011;113:736-745.
3. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement (N Y)*. 2013;9:63-75 e2.
4. Cao Q, Tan CC, Xu W, et al. The Prevalence of Dementia: a Systematic Review and Meta-Analysis. *J Alzheimers Dis : JAD*. 2020;73:1157-1166.
5. Andersen K, Launer LJ, Dewey ME, et al. Gender differences in the incidence of AD and vascular dementia: the EURODEM Studies. EURODEM Incidence Research Group. *Neurology*. 1999;53:1992-1997.
6. Erol R, Brooker D, Peel E. Alzheimer's Disease International. Women and Dementia: a global research review. 2015.
7. Fratiglioni L, Viitanen M, von Strauss E, Tontodonati V, Herlitz A, Winblad B. Very old women at highest risk of dementia and Alzheimer's disease: incidence data from the Kungsholmen Project, Stockholm. *Neurology*. 1997;48:132-138.
8. Chene G, Beiser A, Au R, et al. Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. *Alzheimers Dement (N Y)*. 2015;11:310-320.
9. Li R, Singh M. Sex differences in cognitive impairment and Alzheimer's disease. *Front Neuroendocrinol*. 2014;35:385-403.
10. Snyder HM, Asthana S, Bain L, et al. Sex biology contributions to vulnerability to Alzheimer's disease: a think tank convened by the Women's Alzheimer's Research Initiative. *Alzheimers Dement (N Y)*. 2016;12:1186-1196.
11. Ferretti MT, Iulita MF, Cavedo E, et al. Sex differences in Alzheimer disease - the gateway to precision medicine. *Nat Rev Neurol*. 2018;14:457-469.
12. Tom SE, Hubbard RA, Crane PK, et al. Characterization of dementia and Alzheimer's disease in an older population: updated incidence and life expectancy with and without dementia. *Am J Public Health*. 2015;105:408-413.
13. World Health Organization. The Global Health Observatory. Life expectancy and Healthy life expectancy. *World Health Statistics*. 2020. Accessed October 27, 2020
14. Erostat. Eurostat: Life expectancy at birth, 1980-2016. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Mortality_and_life_expectancy_statistics
15. Sindi S, Mangialasche F, Kivipelto M. Advances in the prevention of Alzheimer's Disease. *F1000prime reports*. 2015;7:50.
16. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet*. 2017;390:2673-2734.
17. Bretsky PM, Buckwalter JG, Seeman TE, et al. Evidence for an interaction between apolipoprotein E genotype, gender, and Alzheimer disease. *Alzheimer Dis Assoc Disord*. 1999;13:216-221.
18. Altmann A, Tian L, Henderson VW, Greicius MD. Alzheimer's Disease Neuroimaging Initiative I. Sex modifies the APOE-related risk of developing Alzheimer disease. *Ann Neurol*. 2014;75:563-573.
19. Payami H, Zareparsi S, Montee KR, et al. Gender difference in apolipoprotein E-associated risk for familial Alzheimer disease: a possible clue to the higher incidence of Alzheimer disease in women. *Am J Hum Genet*. 1996;58:803-811.
20. Mielke MM. Sex and Gender Differences in Alzheimer's Disease Dementia. *Psychiatr Times*. 2018;35:14-17.
21. Nebel RA, Aggarwal NT, Barnes LL, et al. Understanding the impact of sex and gender in Alzheimer's disease: a call to action. *Alzheimers Dement (N Y)*. 2018;14:1171-1183.
22. Kim MY, Kim K, Hong CH, Lee SY, Jung YS. Sex differences in cardiovascular risk factors for dementia. *Biomol Ther (Seoul)*. 2018;26:521-532.
23. Ferretti MT, Martinkova J, Biskup E, et al. Sex and gender differences in Alzheimer's disease: current challenges and implications for clinical practice: position paper of the Dementia and Cognitive

Disorders Panel of the European Academy of Neurology. *Eur J Neurol*. 2020;27:928-943.
24. Stern Y, Arenaza-Urquijo EM, Bartres-Faz D, et al. Whitepaper: defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimers Dement (N Y)*. 2018.
25. Andrew MKT. The puzzle of sex, gender and Alzheimer's disease: why are women more often affected than men? *Women's Health*. 2018;14:1-8.
26. Ewers M. Reserve in Alzheimer's disease: update on the concept, functional mechanisms and sex differences. *Curr Opin Psychiatry*. 2020;33:178-184.
27. Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. *Clin Epidemiol*. 2014;6:37-48.
28. Apostolova LG, Dinov ID, Dutton RA, et al. 3D comparison of hippocampal atrophy in amnestic mild cognitive impairment and Alzheimer's disease. *Brain*. 2006;129:2867-2873.
29. Beckman N, Waern M, Gustafson D, Skoog I. Secular trends in self reported sexual activity and satisfaction in Swedish 70 year olds: cross sectional survey of four populations, 1971-2001. *BMJ*. 2008;337:a279.
30. Sindi S, Hagman G, Hakansson K, et al. Midlife Work-Related Stress Increases Dementia Risk in Later Life: the CAIDE 30-Year Study. *J Gerontol B Psychol Sci Soc Sci*. 2017;72:1044-1053.
31. Fratiglioni L, Grut M, Forsell Y, Viitanen M, WinbladB. Clinical diagnosis of Alzheimer's disease and other dementias in a population survey. Agreement and causes of disagreement in applying Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition, Criteria. *Arch Neurol*. 1992;49:927-932.
32. Sindi S, Kåreholt I., Johansson L, et al. Sleep disturbances and dementia risk: a multicenter study. *Alzheimer's Dement*. 2018;14(10):1235-1242.
33. Puska P. From Framingham to North Karelia: from descriptive epidemiology to public health action. *Prog Cardiovasc Dis*. 2010;53:15-20.
34. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 2015;385:2255-2263.
35. Kivipelto M, Solomon A, Ahtiluoto S, et al. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): study design and progress. *Alzheimers Dement (N Y)*. 2013;9:657-665.
36. Singer JD, Willett JB. It's about time: using discrete-time survival analysis to study duration and the timing of events. *J Educ Stat*. 1993;18:155-195.
37. Allison PD. Discrete-time methods for the analysis of event histories. *Sociol Methodol*. 1982;13:61-98.
38. Genin E, Hannequin D, Wallon D, et al. APOE and Alzheimer disease: a major gene with semi-dominant inheritance. *Mol Psychiatry*. 2011;16:903-907.
39. Rocca WA, Mielke MM, Vemuri P, Miller VM. Sex and gender differences in the causes of dementia: a narrative review. *Maturitas*. 2014;79:196-201.
40. Larson EB, Langa KM. What's the "Take Home" from Research on Dementia Trends?. *PLoS Med*. 2017;14:e1002236.
41. Langa KM. Is the risk of Alzheimer's disease and dementia declining? *Alzheimers Res Ther*. 2015;7:34.
42. Skoog I, Borjesson-Hanson A, Kern S, et al. Decreasing prevalence of dementia in 85-year olds examined 22 years apart: the influence of education and stroke. *Sci Rep*. 2017;7:6136.
43. Gerstorf D, Ram N, Hoppmann C, Willis SL, Schaie KW. Cohort differences in cognitive aging and terminal decline in the Seattle Longitudinal Study. *Dev Psychol*. 2011;47:1026-1041.
44. Schaie KW, Willis SL. The Seattle Longitudinal Study of Adult Cognitive Development. *ISSBD bulletin*. 2010;57:24-29.
45. Hakansson K, Soininen H, Winblad B, Kivipelto M. Feelings of Hopelessness in Midlife and Cognitive Health in Later Life: a Prospective Population-Based Cohort Study. *PLoS One*. 2015;10:e0140261.
46. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396:413-446.
47. da Silva J, Goncalves-Pereira M, Xavier M, Mukaetova-Ladinska EB. Affective disorders and risk of developing dementia: systematic review. *Br J Psychiatry*. 2013;202:177-186.
48. Tolppanen AM, Solomon A, Kulmala J, et al. Leisure-time physical activity from mid- to late life, body mass index, and risk of dementia. *Alzheimers Dement (N Y)*. 2015;11:434-443 e6.
49. Fallah N, Mitnitski A, Middleton L, Rockwood K. Modeling the impact of sex on how exercise is associated with cognitive changes and death in older Canadians. *Neuroepidemiology*. 2009;33:47-54.
50. Clifford A, Bandelow S, Hogervorst E. *The Effects of Physical Exercise on Cognitive Function in the Elderly: A Review. Handbook of cognitive aging: Causes, processes and mechanisms*. New York: Nova Science; 2009:20.
51. Hogervorst E, Clifford A, Stock J, Xin X, Bandelow S. Exercise to prevent cognitive decline and Alzheimer's disease: for whom, when, what, and (most importantly) how much. *J Alzheimers Dis Parkinsonism*. 2012;2:e117.
52. Middleton LE, Barnes DE, Lui LY, Yaffe K. Physical activity over the life course and its association with cognitive performance and impairment in old age. *J Am Geriatr Soc*. 2010;58:1322-1326.
53. Fougère B, Morley J, Arai H, et al. Precision Medicine: the Future Management of Geriatric Conditions. *J Nutr Health Aging*. 2018:1-4.
54. Canevelli M, Quarata F, Remiddi F, et al. Sex and gender differences in the treatment of Alzheimer's disease: a systematic review of randomized controlled trials. *Pharmacol Res*. 2017;115:218-223.
55. Rocca WA, Grossardt BR, Shuster LT. Oophorectomy, estrogen, and dementia: a 2014 update. *Mol Cell Endocrinol*. 2014;389:7-12.
56. Merlo S, Spampinato SF, Sortino MA. Estrogen and Alzheimer's disease: still an attractive topic despite disappointment from early clinical results. *Eur J Pharmacol*. 2017;817:51-58.
57. Imtiaz B, Tuppurainen M, Tiihonen M, et al. Oophorectomy, hysterectomy, and risk of Alzheimer's disease: a nationwide case-control study. *J Alzheimers Dis : JAD*. 2014;42:575-581.

How to cite this article: Sindi S, Kåreholt I, Ngandu T, et al. Sex differences in dementia and response to a lifestyle intervention: Evidence from Nordic population-based studies and a prevention trial. *Alzheimer's Dement*. 2021;17:1166–1178. https://doi.org/10.1002/alz.12279