

# Sex Differences in Cognitive Functioning with Aging in the Netherlands

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## Keywords

Aging · Cognitive function · Cohort effect · Longitudinal study · Sex

## Abstract

**Introduction:** Dementia prevalence in older women is higher than that in men. The purpose of the present study was to investigate whether there is a female disadvantage in cognitive functioning at adult age and/or whether a female disadvantage develops with age. **Methods:** Data of 5,135 women and 4,756 men from the Longitudinal Aging Study Amsterdam (LASA) and the Doetinchem Cohort Study (DCS) were used. In the LASA, memory, processing speed, fluid intelligence, and global cognitive function were measured every 3–4 years since 1992 in persons aged 55+ years for up to 23 years. In the DCS, memory, processing speed, cognitive flexibility, and global cognitive function were measured every 5 years since 1995 in persons aged 45+ years for up to 20 years. Sex differences in cognitive aging were analyzed using linear mixed models and also examined by the 10-year birth cohort or level of education. **Results:** Women had a better memory, processing speed, flexibility, and, in the DCS only, global

cognitive function than men ( $p$ 's < 0.01). However, women showed up to 10% faster decline in these cognitive domains, except for flexibility, where women showed 9% slower decline. In the LASA, women scored poorer on fluid intelligence ( $p$  < 0.01), but their decline was 10% slower than that in men. Female advantage was larger in later born cohorts; adjustment for the educational level increased the female advantage. **Conclusion:** Women have better memory and processing speed than men at middle age. This female advantage becomes smaller with aging and has increased in more recent birth cohorts.

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## Introduction

In 2016, in the Netherlands, the number of women who died with dementia was twice the number of men who died with dementia [1]. Also, the prevalence of dementia is almost twice as high in older women than in men of the same age [2]. Dementia is usually preceded by a long period of decline in cognitive functions [3]. Based on a continuum from healthy cognitive function to de-

mentia, a lower cognitive function (cognitive reserve) and/or a steeper cognitive decline increases the risk of dementia. The purpose of the present study was to investigate whether there is a female disadvantage in cognitive functioning at adult age and/or whether a female disadvantage develops with age that can explain the sex differences in dementia prevalence at older age.

Sex differences in cognitive function at adult age are well documented: women score higher on cognitive tasks that require verbal processing, while men score higher on tasks that require visuospatial processing [4]. A systematic review showed that sex differences remain similar between the age of 60–80 years, but that sex differences in cognitive decline may occur after the age of 80 years, although the directions of the associations found were sometimes contradictory [5]. Since this review, some more longitudinal studies showed inconsistent results on sex differences in cognitive decline: either no difference in the rate of cognitive decline between men and women [6], or a steeper decline for men than for women [7, 8]. The longest follow-up in these studies was 17 years [5–8]. In a recent US study with up to 21 years of follow-up, women had faster declines in global function and executive function, but there was no difference in memory decline between men and women [9]. In this latter study, only few repeated measurements were available for memory. In the present study, we were able to examine cognitive change over a longer period of time (up to 23 years), based on a higher number of repeated cognitive measurements and up to a higher age (100 years), in 2 large Dutch cohort studies. Since secular trends in economic prosperity and gender equity in educational chances may influence sex differences in cognitive function [4, 10], we also studied whether sex differences in cognitive functioning differ between different birth cohorts and between different levels of education. We expect that secular trends have improved the average cognitive function of women more than that of men, as the educational opportunities of women have improved in the course of the 20th century due to women's emancipation [11] and education is a key predictor of later life cognitive functioning.

## Methods

We used data from 2 large Dutch aging cohorts: the Longitudinal Aging Study Amsterdam (LASA) [12–14] and the Doetinchem Cohort Study (DCS) [15, 16]. Both studies have been conducted in line with the Declaration of Helsinki. The LASA has been approved by the Medical Ethics Committee of the VU University medical center and the DCS by the external

Medical Ethics Committee of the Netherlands Organization for Applied Scientific Research and the Medical Ethics Committee of the University of Utrecht. All participants gave written informed consent.

The LASA started in 1992 with 3,107 participants aged 54–85 years from 3 birth cohorts (1908–1917, 1918–1927, and 1928–1937). Ten years later, 1,002 persons aged 54–65 years (born between 1938 and 1947) were added, and in 2012, 1,023 persons aged 54–65 years (born between 1948 and 1957) were added to the ongoing study. Participants are re-measured every 3–4 years. From the LASA, 2,653 women and 2,469 men aged 54–85 years at baseline could be included in our study (see online suppl. Table 1; for all online suppl. material, see [www.karger.com/doi/10.1159/520318](http://www.karger.com/doi/10.1159/520318)). The median follow-up was 6 years and ranged from 0 to 23 years (1–8 repeated measurements).

The DCS started in 1987–1991 with an age- and sex-stratified sample of 12,404 men and women aged 20–59 years from the town of Doetinchem. A random selection of 7,769 of these participants was re-invited 6 years later and subsequently has been invited every 5 years. Halfway the second examination round (from 1995 onward), cognitive testing was introduced for participants aged 45 years and over. From the DCS, 2,482 women and 2,287 men aged 45–82 years at baseline, born between 1928 and 1967, were included (see online suppl. Table 2). The median follow-up was 10 years and ranged from 0 to 20 years (1–5 repeated measurements).

### *Cognitive Function*

In the LASA 4 cognitive tests have been repeatedly carried out: a 15-word learning test [17], a letter substitution task [18], the Raven Colored Progressive Matrices [19] (up to and including the 6th measurement round), and the Mini-Mental State Examination (MMSE) [20]. In the DCS, 4 cognitive tests are repeatedly carried out: a 15-word learning test [21], a letter digit substitution task [22], the Stroop test [23], and a fluency test [24]. Details on these cognitive tests are included as online supplementary material.

### *Cognitive Domain Scores*

In the LASA, memory function was calculated as the average of the total score on the immediate recalls, the maximum score on the 3 immediate recalls, and the score on the delayed recall of the 15-word learning test. Information processing speed was calculated as the average score on the 3 trials of the letter substitution test. Fluid intelligence was calculated as the total score on sections A and B of the Raven Progressive Matrices. Global cognitive function was the maximum score on the MMSE, either based on the subtraction or the spelling backward item.

In the DCS, memory function was calculated as the average of the total score on the immediate recalls, the maximum score on the 3 immediate recalls, and the score on the delayed recall of the 15-word learning test. Information processing speed was calculated as the average of the first 2 trials of the Stroop test (reading and color naming) and the score on the letter digit substitution task. Flexibility was calculated as the score on the third trial of the Stroop test (naming ink color). All tests are taken together to calculate a measure for global cognitive function (average z-score on the total of immediate recalls, delayed recall, third trial of the Stroop test (naming ink color), letter digit substitution test, and the fluency test) [25].

### Demographic Characteristics

For all participants in both the LASA and DCS, date of birth, age, sex, and the highest attained level of education are ascertained. Based on birth date, participants were categorized in 10-year birth cohorts: 1908–1917, 1918–1927, 1928–1937, 1938–1947, 1948–1957, or 1958–1967. The highest attained level of education was categorized in 3 levels, based on the distribution in LASA: low (elementary education or less), medium (lower vocational education or general intermediate education), and high (intermediate vocational education, general secondary education, or higher).

### Statistics

In order to compare cognitive function between men and women, reducing the impact of learning effects on cognitive tests, all cognitive data were corrected for the number of cognitive measurements so far, based on the association between the number of measurements (classes) and cognitive function in a linear longitudinal regression model adjusting for age, age<sup>2</sup>, sex, and level of education. After adjusting for the number of measurements, all cognitive data, except for the MMSE scores, were standardized into z-scores based on the mean and standard deviation of the first cognitive measurements of all participants in the study (baseline).

### Sex Differences

To study sex differences in (mean level of) cognitive function, cognitive test scores were included in mixed model analyses with random intercept for the individuals, random slope for age (since this increased model fit significantly, as tested by comparing  $-2LL$  between model without and with random slope for age), and an unstructured covariance matrix. Independent variables in these analyses on differences in the level between women and men were sex, age, and age<sup>2</sup> (model 1). If the estimate for sex is statistically significant in this model, positive values denote that women perform better than men do. Negative values denote that men perform better than women do.

Based on this model, difference in cognitive age (expressed in years) was calculated in order to facilitate the interpretation of the differences between men and women at a certain calendar age. At what calendar age is the cognitive function of men at the same level as the cognitive function of women at the age of 65 years? The difference in calendar age is used as an indicator for the difference in cognitive age between men and women (see also online suppl. Fig. 1). So if the cognitive function in women at age 65 years equals the cognitive function of men at age 62 years, the difference in cognitive age is 3 years [26].

To test for sex differences in cognitive decline with aging, the interaction term of sex and age was added. Independent variables in these analyses on differences in cognitive decline with aging were sex, age, age<sup>2</sup>, sex  $\times$  age, and sex  $\times$  age<sup>2</sup> (model 2). If an interaction term of sex and age is significant in this model, positive values denote that the decline in cognitive function with aging is stronger in men than that in women. Negative values denote that the decline with aging is stronger in women than that in men. Sex  $\times$  age<sup>2</sup> was only included if this interaction term was significantly associated with cognitive function at  $p < 0.05$ .

Based on these models, difference in cognitive aging was calculated as difference in cognitive decline (in percentage) between men and women between ages 65–75 years. If the interaction term of sex and age was significant in model 2, this model was used to describe and plot sex differences in cognitive function with aging.

**Table 1.** Baseline characteristics (participants at their first cognitive measurement)

	Women	Men
LASA	<i>n</i> = 2,654 (52%)	<i>n</i> = 2,469
Mean age (SD), years	66.5 (8.7)	66.7 (8.8)
Range	54–88	54–88
Level of education, %		
Low*	39.8	25.8
Medium	32.6	31.3
High	27.6	42.9
Birth cohort, %		
1908–1917	21.6	23.5
1918–1927	19.3	18.3
1928–1937	19.4	19.1
1938–1947	19.8	19.1
1948–1957	19.9	20.1
DCS	<i>n</i> = 2,482 (52%)	<i>n</i> = 2,287
Mean age (SD), years	55.2 (6.6)	55.5 (6.6)
Range	45–77	45–82
Level of education, %		
Low*	6.7	5.7
Medium	48.2	31.9
High	45.1	62.4
Birth cohort, %		
1928–1937	17.6	19.1
1938–1947	27.9	31.1
1948–1957	37.7	36.5
1958–1967	16.9	13.3

Baseline characteristics are given over all first measurements (t0). LASA, Longitudinal Aging Study Amsterdam; DCS, Doetinchem Cohort Study. \* Level of education was classified in 3 levels: Low, elementary education or less; Medium, lower vocational education or general intermediate education; High, intermediate vocational education, general secondary education, or higher (higher vocational education/college education/university education).

Otherwise, model 1 was used. If model 2 was used, so decline with aging differed between men and women, it was then examined at which age the sex differences were no longer statistically significantly different.

Associations were considered to be statistically significant at  $p < 0.05$ . Age was centered at 55 years in all analyses on sex differences, in order to present a realistic sex difference (at age 55 years), especially when cognitive decline with aging differs between men and women.

### Differences between Birth Cohorts and Levels of Education

Sex differences in *level of cognitive function* were tested between birth cohorts or between educational levels by adding an interaction term of sex and the subgroups to model 1 (e.g., sex\*education). Sex differences in *cognitive decline with aging* between subgroups were tested by adding an interaction term of sex, age, and the subgroups (3-way interaction: e.g., age\*sex\*education) to model 2. Sex differences in cognitive function and cognitive decline with aging within subgroups were calculated in subgroup-stratified analyses.

**Table 2.** Differences in the level of cognitive functioning and cognitive decline with aging between men and women, from middle to old age (range 55–104 years), and by birth cohort and level of education in LASA

	Memory function (z-score)		Information processing speed (z-score)		Fluid intelligence (z-score)		Global cognitive function (MMSE score)	
	model 1 (level of cognitive functioning)	model 2 (cognitive decline)	model 1 (level of cognitive functioning)	model 2 (cognitive decline)	model 1 (level of cognitive functioning)	model 2 (cognitive decline)	model 1 (level of cognitive functioning)	model 2 (cognitive decline)
Overall	(n = 4,632, 14,411 observations)	(n = 4,579, 14,236 observations)	(n = 3,860, 12,041 observations)	(n = 5,123, 17,319 observations)				
Sex <sup>†</sup>	<b>0.422</b> [0.375, 0.469]	<b>0.483</b> [0.409, 0.556]	<b>0.106</b> [0.058, 0.154]	0.185 [0.122, 0.248]	<b>-0.143</b> [-0.194, -0.092]	<b>-0.216</b> [-0.296, -0.136]	0.002 [-0.110, 0.114]	0.044 [-0.132, 0.219]
Sex × age	<b>-0.004</b> [-0.008, -0.000]	<b>-0.006</b> [-0.009, -0.003]		<b>-0.006</b> [-0.009, -0.003]	<b>0.005</b> [0.001, 0.009]			<b>-0.004</b> [-0.017, 0.009]
By birth cohort								
1908–1917								
Sex	<b>0.30</b> [0.20, 0.40] <sup>ab</sup>	0.37 [-0.08, 0.81]	-0.03 [-0.14, 0.07] <sup>d</sup>	-0.00 [-0.35, 0.35]	<b>-0.12</b> [-0.23, -0.01]	-0.02 [-0.49, 0.45]	-0.14 [-0.56, 0.29]	0.49 [-1.49, 2.46]
Sex × age		-0.00 [-0.02, 0.01]		-0.00 [-0.01, 0.01]		-0.00 [-0.02, 0.01]		<b>-0.03</b> [-0.10, 0.05] <sup>j</sup>
1918–1927								
Sex	<b>0.47</b> [0.37, 0.58] <sup>a</sup>	<b>0.60</b> [0.37, 0.82]	0.09 [-0.02, 0.20] <sup>e</sup>	0.13 [-0.06, 0.32]	-0.03 [-0.14, 0.08] <sup>hi</sup>	-0.16 [-0.38, 0.07]	0.05 [-0.22, 0.32]	-0.09 [-0.78, 0.60]
Sex × age		-0.01 [-0.02, 0.00]		-0.00 [-0.01, 0.01]		0.01 [-0.00, 0.02]		0.01 [-0.03, 0.05]
1928–1937								
Sex	<b>0.44</b> [0.34, 0.54]	<b>0.44</b> [0.32, 0.57]	0.07 [-0.04, 0.18] <sup>f</sup>	0.12 [-0.00, 0.24]	<b>-0.20</b> [-0.29, -0.10] <sup>h</sup>	<b>-0.21</b> [-0.33, -0.09]	-0.09 [-0.30, 0.13]	-0.16 [-0.44, 0.12]
Sex × age		-0.00 [-0.01, 0.01]		-0.00 [-0.01, 0.00]		0.00 [-0.01, 0.01]		0.01 [-0.01, 0.03] <sup>j</sup>
1938–1947								
Sex	<b>0.36</b> [0.26, 0.46] <sup>c</sup>	<b>0.39</b> [0.26, 0.52]	<b>0.11</b> [0.00, 0.21] <sup>g</sup>	<b>0.18</b> [0.07, 0.30]	<b>-0.22</b> [-0.31, -0.12] <sup>i</sup>	<b>-0.25</b> [-0.39, -0.11]	-0.07 [-0.32, 0.17]	-0.04 [-0.35, 0.27]
Sex × age		-0.00 [-0.01, 0.01]		<b>-0.01</b> [-0.02, -0.00]		0.01 [-0.01, 0.02]		-0.00 [-0.03, 0.02]
1948–1957								
Sex	<b>0.55</b> [0.44, 0.66] <sup>bc</sup>	<b>0.54</b> [0.33, 0.75]	<b>0.30</b> [0.20, 0.40] <sup>defg</sup>	<b>0.24</b> [0.09, 0.39]	#		0.19 [-0.02, 0.40]	<b>0.42</b> [0.01, 0.83]
Sex × age		0.00 [-0.02, 0.03]		0.01 [-0.01, 0.03]				<b>-0.03</b> [-0.09, 0.02]
By educational level								
Low								
Sex	<b>0.45</b> [0.36, 0.53]	<b>0.61</b> [0.45, 0.76]	<b>0.15</b> [0.07, 0.24] <sup>k</sup>	<b>0.32</b> [0.18, 0.45]	0.03 [-0.06, 0.12]	0.12 [-0.06, 0.30]	<b>0.32</b> [0.03, 0.60]	<b>0.53</b> [0.02, 1.03]
Sex × age		<b>-0.01</b> [-0.02, -0.00]		-0.01 [-0.01, -0.00]		-0.00 [-0.01, 0.00] <sup>m</sup>		<b>-0.01</b> [-0.04, 0.01] <sup>n</sup>
Medium								
Sex	<b>0.55</b> [0.48, 0.63]	<b>0.40</b> [0.24, 0.56]	<b>0.34</b> [0.27, 0.42] <sup>kl</sup>	<b>0.39</b> [0.29, 0.49]	0.01 [-0.07, 0.09]	<b>-0.15</b> [-0.27, -0.02]	<b>0.26</b> [0.09, 0.42]	0.04 [-0.22, 0.31]
Sex × age		<b>0.03</b> [0.01, 0.04]		-0.00 [-0.01, 0.00]		0.01 [0.00, 0.02] <sup>m</sup>		<b>0.02</b> [0.00, 0.04] <sup>n</sup>
Sex × age <sup>2</sup>		<b>-0.00</b> [-0.00, -0.00]						
High								
Sex	<b>0.54</b> [0.46, 0.61]	<b>0.60</b> [0.49, 0.71]	<b>0.18</b> [0.11, 0.26] <sup>l</sup>	<b>0.25</b> [0.16, 0.34]	<b>-0.07</b> [-0.14, -0.00]	<b>-0.14</b> [-0.24, -0.03]	0.12 [-0.00, 0.24]	0.09 [-0.13, 0.30]
Sex × age		<b>-0.01</b> [-0.01, -0.00]		<b>-0.01</b> [-0.01, -0.00]		0.01 [-0.00, 0.01]		0.00 [-0.01, 0.02]

Estimates in bold are statistically significant at  $p < 0.05$ ; estimates with same superscript letters are significantly different at  $p < 0.05$  (between comparable models only). LASA, Longitudinal Aging Study Amsterdam; MMSE, Mini-Mental State Examination. <sup>†</sup> Sex differences are presented as average (95% CI) and represent the average difference in cognitive function between men and women, regardless of age (model 1) or at age 55 years (model 2). Positive values represent better scores (sex) or less decline for every year of aging (sex × age)<sup>2</sup> for women compared to men. Sex differences are adjusted for age and age squared, with age centered at age 55 years. <sup>‡</sup> Fluid intelligence was not assessed in the latest birth cohort. For stratified analyses on the latest birth cohort (1948–1957), no random slope was included in the model.

### *Sensitivity Analyses*

In order to test whether menopause influenced results, analyses for DCS were repeated, excluding participants younger than 55 years. Mixed model analyses are able to deal with missing values, based on the assumption that missings are at random. Since missings due to attrition are likely not at random, we repeated our analyses based on data up to age 80 years (LASA and DCS), diminishing attrition not at random due to, e.g., illness and death, and tested whether sex differences were different between participants who did and did not participate for 10 years (LASA) or in the most recent measurement round (DCS).

## **Results**

In the LASA, the average age at baseline was 66 years and in the DCS, 55 years. In both cohorts, there were about as many men as women. In all birth cohorts, men were higher educated than women and each subsequent birth cohort was higher educated than the previous one (see online suppl. Table 3). More details on demographic characteristics of the study population are presented in Table 1.

### *Sex Differences in Cognitive Function*

#### **Memory**

Women scored better than men on memory in the LASA and DCS (Tables 2, 3). At the age of 65 years, women were cognitively >10 years younger than men. This female advantage became smaller with aging due to stronger decline in women (9% between ages 65–75 years). Despite this convergence, the sex difference in memory remained statistically significant until after the age of 85–90 years (see also Fig. 1).

#### **Information Processing Speed**

In the LASA and DCS, women scored better than men on information processing speed (Tables 2, 3). At the age of 65 years, women were cognitively 3 years younger than men. This female advantage became smaller with aging due to stronger decline in women (7–10% between ages 65–75 years). Due to this convergence, the sex difference in processing speed lost its statistical significance between the ages of 75–80 years (see also Fig. 1).

#### **Fluid Intelligence**

Women scored lower than men on fluid intelligence (Table 2). At the age of 65 years, women were cognitively 4 years older than men. This female disadvantage became smaller with aging due to smaller decline in women (10% between ages 65 and 75 years). The sex difference in fluid intelligence lost its statistical significance between the age of 80–85 years (see also Fig. 1).

### *Cognitive Flexibility*

Women scored better than men on cognitive flexibility (Table 3). At the age of 65 years, women were cognitively 3 years younger than men. This female advantage further increased with aging due to smaller decline in women (9% between ages 65 and 75 years, see also Fig. 1).

### *Global Cognitive Function*

In the LASA, no significant differences in global cognitive function or decline in global cognitive function (based on MMSE) with aging were observed between men and women (Table 2; Fig. 1). In the DCS, women scored better than men on global cognitive function (based on all cognitive tests, Table 3). At the age of 65 years, women were cognitively 4 years younger than men. This female advantage became smaller with aging due to stronger decline in women (10% between ages 65 and 75 years). Despite this convergence, the sex difference in global cognitive function in the DCS remained statistically significant until after the age of 85 years (see also Fig. 1).

### *Sex Differences by Birth Cohorts*

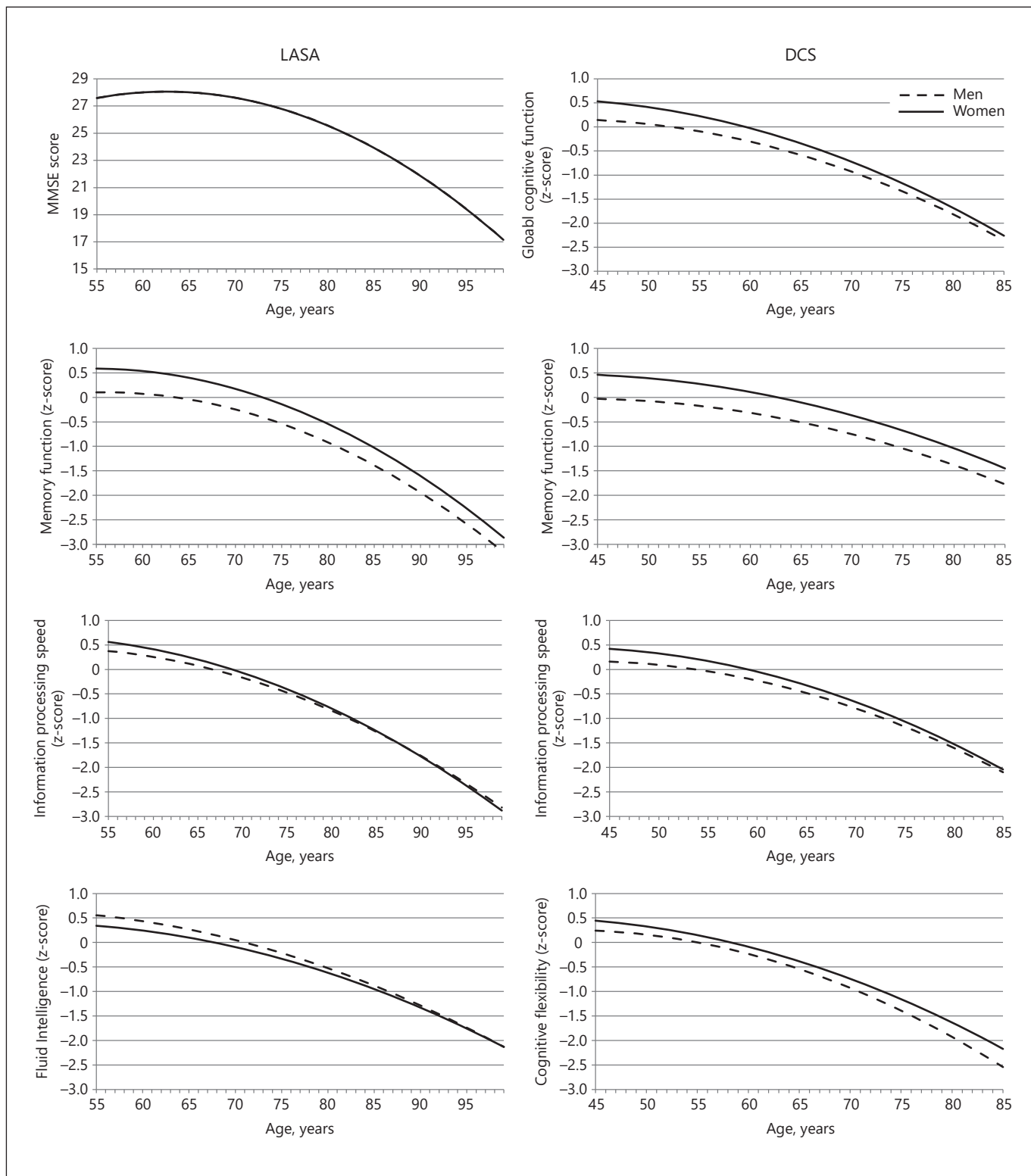
Female advantage was larger in the most recent birth cohort than the earlier birth cohorts for memory and information processing speed (Tables 2, 3), and global cognitive function (in DCS only, Table 3). In analyses stratified for birth cohort, cognitive decline was not consistently different between men and women, or between birth cohorts.

### *Sex Differences by Educational Levels*

Sex differences in the level of cognitive function were not statistically different between levels of education, except for information processing speed in LASA (Tables 2, 3). For processing speed, the female advantage was significantly larger in the medium educated participants than in the low- and high-educated groups. The female advantage in cognitive function within different levels of education appeared larger than the overall female advantage. Moreover, sex differences in fluid intelligence were no longer present, while for global cognitive function in the LASA, a female advantage appeared in stratified analyses. Also, for fluid intelligence, cognitive flexibility, and global cognitive function (LASA only), women in the medium educated group showed less cognitive decline than those in the low-educated group (Tables 2, 3).

### *Sensitivity Analyses*

Analyses excluding participants younger than 55 years showed similar or smaller estimates for overall sex differ-



**Fig. 1.** Cognitive functions with aging for men and women in the LASA (plotted for age 55–99 years) and DCS (plotted for age 45–85 years). Note that MMSE scores with aging of men and women in LASA are similar, and therefore, only 1 line is visible in the figure. LASA, Longitudinal Aging Study Amsterdam; DCS, Doetinchem Cohort Study; MMSE, Mini-Mental State Examination.

**Table 3.** Differences in the level of cognitive functioning and cognitive decline with aging between men and women, from middle to old age (range 45–85 years) and by birth cohort and level of education in DCS

	Memory function (z-score)		Information processing speed (z-score)		Cognitive flexibility (z-score)		Global cognitive function (z-score)	
	model 1 (level of cognitive functioning)	model 2 (cognitive decline)	model 1 (level of cognitive functioning)	model 2 (cognitive decline)	model 1 (level of cognitive functioning)	model 2 (cognitive decline)	model 1 (level of cognitive functioning)	model 2 (cognitive decline)
Overall	(n = 4,763, 12,883 observations)	(n = 4,751, 12,834 observations)	(n = 4,754, 12,838 observations)	(n = 4,742, 12,756 observations)				
Sex <sup>†</sup>	<b>0.431</b> [0.382, 0.480]	<b>0.447</b> [0.396, 0.499]	<b>0.194</b> [0.143, 0.246]	<b>0.209</b> [0.156, 0.261]	<b>0.160</b> [0.110, 0.209]	<b>0.149</b> [0.098, 0.200]	<b>0.292</b> [0.242, 0.342]	<b>0.317</b> [0.265, 0.368]
Sex × age	<b>-0.004</b> [-0.008, -0.000]	<b>-0.005</b> [-0.008, -0.002]			<b>0.000</b> [0.000, 0.001]	<b>0.000</b> [0.000, 0.003]		<b>-0.007</b> [-0.010, -0.004]
Sex × age <sup>2</sup>								
By birth cohort								
1928–1937								
Sex	<b>0.24</b> [0.12, 0.35] <sup>g</sup>	<b>0.35</b> [0.16, 0.54]	-0.04 [-0.17, 0.09] <sup>kl</sup>	<b>0.35</b> [0.03, 0.68]	0.08 [-0.05, 0.20]	0.30 [-0.07, 0.67]	0.00 [-0.12, 0.12] <sup>abc</sup>	0.09 [-0.07, 0.26]
Sex × age		-0.01 [-0.02, 0.00]		<b>-0.05</b> [-0.09, -0.01]		-0.04 [-0.08, 0.01]		-0.01 [-0.02, 0.00]
Sex × age <sup>2</sup>				<b>0.00</b> [0.00, 0.00]		<b>0.00</b> [0.00, 0.00]		
1938–1947								
Sex	<b>0.48</b> [0.39, 0.57] <sup>e</sup>	<b>0.48</b> [0.37, 0.59]	<b>0.21</b> [0.11, 0.30] <sup>j</sup>	<b>0.21</b> [0.11, 0.31]	<b>0.18</b> [0.09, 0.27]	<b>0.15</b> [0.05, 0.25]	<b>0.33</b> [0.24, 0.42] <sup>a</sup>	<b>0.36</b> [0.26, 0.46]
Sex × age		0.01 [-0.01, 0.02]		-0.00 [-0.01, 0.00] <sup>i</sup>		0.01 [-0.00, 0.01] <sup>lm</sup>		<b>-0.01</b> [-0.01, -0.00]
Sex × age <sup>2</sup>		-0.00 [-0.00, -0.00]						
1948–1957								
Sex	<b>0.43</b> [0.35, 0.50] <sup>h</sup>	<b>0.43</b> [0.35, 0.50]	<b>0.23</b> [0.15, 0.31] <sup>j</sup>	<b>0.22</b> [0.14, 0.30]	<b>0.15</b> [0.07, 0.23]	<b>0.15</b> [0.07, 0.23]	<b>0.31</b> [0.23, 0.39] <sup>bd</sup>	<b>0.30</b> [0.22, 0.38]
Sex × age		0.00 [-0.01, 0.01]		<b>-0.01</b> [-0.01, -0.00] <sup>i</sup>		-0.00 [-0.01, 0.00] <sup>lm</sup>		<b>-0.01</b> [-0.01, -0.00]
1958–1967								
Sex	<b>0.57</b> [0.43, 0.70] <sup>h</sup>	<b>0.56</b> [0.42, 0.70]	<b>0.32</b> [0.18, 0.45] <sup>k</sup>	<b>0.32</b> [0.18, 0.46]	<b>0.19</b> [0.07, 0.31]	<b>0.18</b> [0.06, 0.31]	<b>0.45</b> [0.32, 0.58] <sup>cd</sup>	<b>0.45</b> [0.32, 0.58]
Sex × age		-0.00 [-0.04, 0.03]		0.00 [-0.02, 0.03]		-0.00 [-0.02, 0.02]		0.00 [-0.03, 0.03]
By educational level								
Low								
Sex	<b>0.52</b> [0.33, 0.72]	<b>0.54</b> [0.29, 0.80]	<b>0.30</b> [0.03, 0.56]	<b>0.36</b> [0.06, 0.65]	<b>0.38</b> [0.13, 0.63] <sup>a</sup>	<b>0.45</b> [0.16, 0.74]	<b>0.41</b> [0.21, 0.62]	<b>0.56</b> [0.31, 0.80]
Sex × age		-0.00 [-0.02, 0.01]		-0.01 [-0.03, 0.01]		-0.01 [-0.03, 0.01] <sup>r</sup>		<b>-0.02</b> [-0.03, -0.00]
Medium								
Sex	<b>0.48</b> [0.41, 0.56]	<b>0.48</b> [0.40, 0.56]	<b>0.32</b> [0.24, 0.40] <sup>p</sup>	<b>0.34</b> [0.25, 0.42]	<b>0.24</b> [0.16, 0.32]	<b>0.22</b> [0.14, 0.30]	<b>0.38</b> [0.30, 0.45]	<b>0.40</b> [0.32, 0.48]
Sex × age		-0.00 [-0.01, 0.01]		-0.00 [-0.01, 0.00]		<b>0.01</b> [0.00, 0.01] <sup>r</sup>		<b>-0.01</b> [-0.01, -0.00]
High								
Sex	<b>0.52</b> [0.45, 0.58]	<b>0.54</b> [0.47, 0.60]	<b>0.23</b> [0.17, 0.29] <sup>p</sup>	<b>0.24</b> [0.18, 0.30]	<b>0.20</b> [0.14, 0.26] <sup>a</sup>	<b>0.19</b> [0.13, 0.25]	<b>0.41</b> [0.35, 0.47]	<b>0.43</b> [0.36, 0.49]
Sex × age		<b>-0.01</b> [-0.01, -0.00]		<b>-0.00</b> [-0.01, -0.00]		-0.00 [-0.01, 0.00]		<b>-0.01</b> [-0.01, -0.00]
Sex × age <sup>2</sup>						<b>0.00</b> [0.00, 0.00]		

Estimates in bold are statistically significant at  $p < 0.05$ ; estimates with same superscript letters are significantly different at  $p < 0.05$  (between comparable models only). For stratified analyses on the latest birth cohort (1958–1967), no random slope was included in the model. DCS, Doetinchem Cohort Study. <sup>†</sup> Sex differences are presented as average [95% CI] and represent the average difference in cognitive function between men and women, regardless of age (model 1) or at the age of 55 years (model 2). Positive values represent better scores (sex) or less decline for every year of aging (sex × age and sex × age<sup>2</sup>) for women than men. Sex differences are adjusted for age and age squared, with age centered at the age of 55 years.

ences in cognitive function, but sex differences in cognitive change were larger for memory, and decline in flexibility was now significantly larger in men than that in women (online suppl. Table 6). Analyses on data from participants up to 80 years old yielded comparable results to those based on all available data (online suppl. Table 7). In the LASA, sex differences in memory function, but not memory decline, were larger in the group who remained >10 years in the study than persons who dropped out earlier. In the DCS, although persons who did not participate in the most recent measurement round had worse cognitive function and declined faster, attrition did not affect sex differences in cognitive function or cognitive decline.

## Discussion

The objective of this study was to investigate sex differences in cognitive function at middle age and in cognitive decline with aging from middle to old age. We observed a female advantage for memory function, information processing speed, and cognitive flexibility; a female disadvantage for fluid intelligence; and no sex differences (in LASA) or a female advantage (in DCS) for global cognitive function. Overall, these sex differences in cognitive function declined with aging, since women showed faster cognitive decline in memory and information processing speed than men. Sex differences in cognitive function were larger in more recent birth cohorts. After adjustment for the educational level, the female advantages were larger, indicating that, particularly in earlier cohorts, the lower average education level of women suppressed part of the sex differences in cognitive functioning.

In our study, men outperformed women in spatial tests (fluid intelligence) and women outperformed men on verbal tests (memory test) and speed tests (substitution test). In an opinion article, Hyde [4] wrote that such differences between men and women existed in psychological research from the 1930s through the 1970s, but that these phenomena may have narrowed over time [4]. In our longitudinal datasets, however, we observed that both the female advantages (memory and information processing speed) as well as the female disadvantage (fluid intelligence) became larger in later birth cohorts. The larger female advantages in more recent birth cohorts may be explained by the fact that inequalities in educational attainment between men and women declined across birth cohorts. However, the increase of the female

disadvantage on fluid intelligence with more recent birth cohort is not easily explained. Based on our results, existing differences between men and women seem to have enlarged over time.

In agreement with the systematic review [5], earlier analyses on sex differences in cognitive decline over, respectively, 6 and 16 years of follow-up in the LASA revealed no significant sex differences [27, 28]. However, in the present study with 23 years of follow-up, we did observe sex differences in cognitive decline in the LASA. The disagreement may be explained by the lack of sex differences in cognitive decline in earlier birth cohorts in the LASA (Table 2). Later studies observed either no sex differences in cognitive decline [6], or, in contrast to our results, observed less cognitive decline among women [7, 8]. For instance, in the English Longitudinal Study of Ageing [8], women aged 50 years and over showed significantly less decline in memory and global cognitive function than men over 8-year period of follow-up. One recent study among US adults [9] showed faster cognitive decline in women for global cognitive function and executive function, but not for memory. In both our cohorts, cognitive decline in memory function as well as processing speed was faster in women than in men. The differences in results can possibly be explained by the fact that we have more repeated measurements, and thus more power, for memory than in Levine's study.

Memory is typically first affected in Alzheimer's disease, while processing speed is, among other domains, affected in vascular dementia. Therefore, the stronger decline in these domains in women may indicate higher risk of these types of dementia at older age in women. We did not investigate sex differences in different types of dementia, but questioned whether sex differences in cognitive function and/or cognitive decline at adult age exist. These may explain sex differences in the total prevalence of dementia, based on the assumption that lower cognitive reserve and/or stronger cognitive decline in general increases the risk of dementia at older age.

In our analyses, with up to 23 years of follow-up, we observed that, in general, sex differences in cognitive functioning became smaller from middle into old age. Cognitive function was modeled as a (nonlinear) function of age, since age is the most important determinant of cognitive functioning [5]. Sex significantly interacted with age on cognitive functioning in the overall analyses. In the stratified analyses, this interaction was less clear and significant in only few birth cohorts (Tables 2, 3). It was not clear whether the sex differences in cognitive decline in the overall models actually were artifacts based on



differences in sex differences between birth cohorts (earlier cohorts showing smaller sex differences in level of cognitive function than later born cohorts). Therefore, ad hoc analyses were performed with birth cohort and educational level as covariates in the models. Now, again, significant interactions of sex and age on cognitive functioning were observed (online suppl. Tables 4, 5), indicating that the sex differences in cognitive decline in our population were not only artifacts but also present within birth cohorts.

Although women outperformed men on memory function and information processing speed, their cognitive functions declined stronger with aging. Among the older population of Cache County (USA), the incidence of AD in women was similar before the age of 85 years, but greater than men after the age of 85 years [29]. In European populations, the prevalence of dementia in men and women start to diverge between the age of 80 and 85 years, to the detriment of women [30]. This age range is about equal to the age range where cognitive functions of men and women start to cross in our analyses (information processing speed and [in DCS] global cognitive function). This disappearance of the female advantage may partly explain the female disadvantage in dementia incidence at very old age.

The difference in cognitive functions between men and women became smaller at higher age, since cognitive decline was larger in women than in men. It was not in the scope of the present study to elucidate on determinants of these differences. Several mechanisms have been postulated to explain sex differences in cognitive decline and/or dementia prevalence: first, estrogen loss in postmenopausal women may explain a stronger cognitive decline with aging, especially in verbal tasks [31]. Typically, we observed a higher rate of cognitive decline in women for memory and processing speed (and the sex differences in these declines were larger after the age of 55 years in DCS), but not for flexibility and fluid intelligence. Therefore, estrogen loss may partly explain the observed sex differences in cognitive decline in the present study. However, one may speculate that women in more recent birth cohort may more often use estrogens as hormone therapy around menopause, but sex differences in cognitive decline between birth cohorts did not reflect such a secular trend. Second, a greater cognitive reserve in men could explain higher dementia prevalence at similar age in women [31]. Individuals with greater cognitive reserve, as reflected in years of education, are better able to cope with AD brain pathology without observable deficits in cognition [32]. This may have been the case in our study.

Especially in earlier birth cohorts, women are lower educated, and may therefore have lower cognitive reserve than men. However, women score higher on most cognitive tests, which is not in line with this explanation. Third, selective survival or competing risk could explain sex differences in cognitive decline. Based on the results in the Framingham study [33], it is questioned whether the higher lifetime risk of dementia for women actually is a female disadvantage. An important competing risk for cognitive decline should not be eliminated, namely, mortality. Men have a lower life expectancy than women because they die younger due to stroke or other cardiovascular diseases. Therefore, it can also be argued that women have a higher risk of dementia due to a lower risk to die from other diseases earlier in life. This hypothesis was verified in more recent analyses on the Framingham study that concluded that selective survival of men with a healthier cardiovascular risk profile and hence lower propensity to dementia might partly explain the higher lifetime risk of dementia/Alzheimer's disease in women [34]. Also in our study, the percentage of (surviving) women increased with longer follow-up, especially at higher ages in the LASA. Our analyses excluding participants over 80 years generated similar, although somewhat larger sex differences in cognitive aging, indicating that healthy survivors narrow the sex differences in cognitive aging. Probably, especially more healthy men with better cognitive health survive and thereby close the cognitive gap between men and women at higher age, when less healthy men have dropped out due to illness or death. Other explanations for sex differences in cognitive decline may be found in differences in lifestyle or differences in cardiovascular risk factors. Another reason could also be a statistical one: since women scored higher at baseline, they have a higher chance to decline stronger over time than men (regression to the mean).

The LASA and DCS are both large population-based cohort studies with a long follow-up period for cognitive function. Therefore, these cohorts provide data over a large age range over different birth cohorts. Sensitive cognitive test batteries produced large ranges of cognitive performance, already from middle age. As all (long-lasting) cohort studies, both the LASA and DCS suffer from (selective) attrition, resulting in relatively healthy cohorts. Nevertheless, also these healthy cohorts showed clear cognitive decline with aging, as well as differences between men and women, birth cohorts, and educational levels. Persons who dropped out had on average lower memory function than persons who did not drop out, but differences between men and women in memory func-

tion and memory decline were not different in the DCS (data not shown). In the LASA, sex differences in memory function, but not memory decline, were larger in the group who remained >10 years in the study than in persons who dropped out earlier. This means that sex differences observed in the LASA may be overestimated due to selective attrition. However, based on our sensitivity analyses on attrition in the DCS, attrition did not affect estimates on sex differences. Since sex differences in the LASA and DCS were comparable, we believe a potential overestimation in LASA was only marginal. Another point is the large difference in the educational level between the DCS and LASA. In the early 20th century, girls, regardless of their cognitive abilities, often did not attend school longer than legally required: up to and including primary school, as was especially seen in our earlier cohorts. With women's emancipation, it also became more common for girls to attend school longer and the level of schooling better matches their cognitive abilities [11]. This trend was confirmed in our population (online suppl. Table 3). In both our cohorts, both the decline in percentage of low-educated participants and the increase in percentage of high-educated participants were larger in women than in men. Thus, as a proxy for cognition, education is better suited in later cohorts than in earlier ones.

In conclusion, at middle age, women had a better cognitive function than men, but most sex differences in cognitive function narrowed with aging. The observation that women decline faster in memory and information processing speed may reflect the sex differences in dementia prevalence as observed at old age. Female advantage was larger in more recent birth cohorts. This may have implications for future sex differences in dementia incidence and prevalence.

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## Statement of Ethics

Both the DCS and LASA have been conducted in line with the Helsinki Declaration. The LASA has been approved by the Medical Ethics Committee of the VU University medical center (reference numbers 92/138, 2002/141 and 2012/361) and the DCS by the external Medical Ethics Committee of the Netherlands Organization for Applied Scientific Research (MEC codes 93/01 and 98/01) and

the Medical Ethics Committee of the University of Utrecht (WMO protocol number 07/233 and METC protocol number 07-233/O). All participants gave written informed consent.

## Conflict of Interest Statement

None of the authors reported a potential conflict of interest.

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## Author Contributions

All authors met the criteria for authorship of the International Committee of Medical Journal Editors. Specific contributions: S.H.O., L.S.S., and H.A.H.W. contributed to conception and acquisition of the work; A.C.J.N. contributed to design, analysis, and drafting; and all authors contributed to interpretation of data, revising, and final approval of the manuscript.

## Data Availability Statement

The data of the Doetinchem Cohort Study pertaining to this manuscript are available upon request. We are unable to place data in a public repository due to legal and ethical constraints. The participants' informed consent did not include consent to public availability of the data. However, the data are available upon request. We advise researchers to contact the corresponding author, who will contact the scientific committee of the Doetinchem Cohort Study.

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