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Female reproductive factors and the likelihood of reaching the age of 90 years. The Netherlands Cohort Study

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ABSTRACT

Objectives: The aim of this study was to prospectively assess the relationship between several reproductive factors in women and the likelihood of reaching the age of 90 years (achieving longevity).
Study design: For this study, data from the oldest birth cohort (1916-17) of the prospective Netherlands Cohort Study (NLCS) were used. These participants filled in a baseline questionnaire in 1986 (at age 68-70 years). Follow-up for vital status information until the age of 90 years (2006-07) was > 99.9% complete.
Main outcome measures: Multivariable-adjusted Cox regression analyses with a fixed follow-up time were based on 2,697 women with complete exposure and co-variable data to calculate risk ratios (RR) of reaching age 90.
Results: No associations were observed between the likelihood of reaching the age of 90 years, and age at menarche, age at menopause, parity, menstrual lifespan, and oral contraceptive use after adjustment for potential confounders. A later age at first childbirth pointed towards a higher chance of achieving longevity (age ≥30 vs. 20-24; RR,1.17; 95%CI,0.98-1.39). Ever-use of hormone replacement therapy (HRT) was significantly associated with a higher chance of achieving longevity compared with never HRT-users, but only in women who had had an early menopause (< 50 years)(RR,1.32; 95% CI, 1.07-1.61).
Conclusion: Age at first childbirth, and ever-use of HRT in women with an early menopause (< 50 years) were associated with the likelihood of reaching the age of 90 years.

1. Introduction

In recent history, women have had a survival advantage over men. Women are almost twice as likely to become a nonagenarian, as compared to men [1]. Estrogen exposure and reproductive processes in women have been considered as a potential explanation for the higher survival rates [2,3]. Based on findings from observational studies, exposure to endogenous steroid hormones has been hypothesized to reduce the risk for cardiovascular disease and -mortality, and to increase the risk for developing several types of cancer (incl. breast, endometrial, and ovarian cancer) [4–7]. The use of exogenous steroid hormones showed no associations with all-cause, cancer, or cardiovascular mortality risk [8–10].

To date, the number of studies that have prospectively assessed the relationship between reproductive factors and longevity is limited [11,12]. Using a prospective cohort, here we aim to assess the relationship between several female reproductive factors and the likelihood of reaching longevity, defined as reaching the age of 90 years.

2. Methods

2.1. Population and study design

For this study data from the Netherlands Cohort Study (NLCS) was used. The NLCS was set up in 1986 as a large prospective cohort study [13]. Baseline data were collected from 62,573 women on lifestyle, dietary habits, reproductive history, and other cancer risk factors using a self-administered questionnaire. In addition, the cohort has been followed-up for mortality. This was done by record linkage to the Central Bureau for Genealogy (CBG) from September 1986 until 1995, and to the municipal population registries (GBA) from 1995 until 2007. Given the case-cohort design usually used in the NLCS [13], the data

Abbreviations: NLCS, Netherlands Cohort Study; RR, Risk Ratio/ Relative risk; 95%CI, 95% Confidence Interval; HRT, Hormone Replacement Therapy; OC, Oral Contraceptives; DAGs, Directed Acyclic Graphs; BMI, Body Mass Index; WHI, Women's Health Initiative

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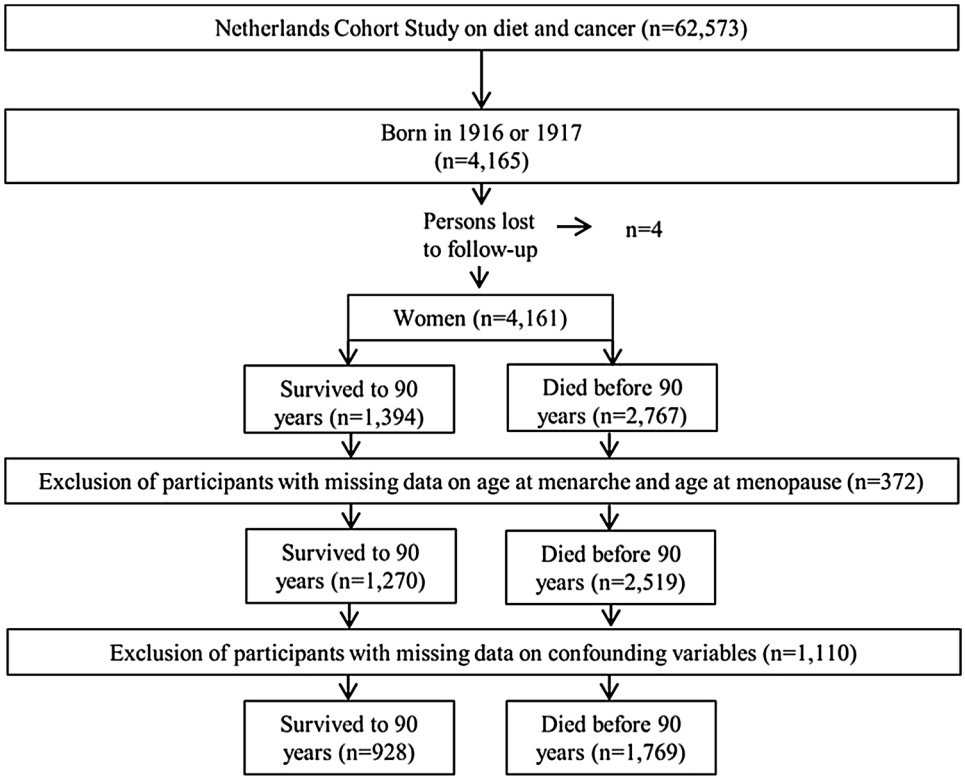

Fig. 1. Flow diagram on the analyses between reproductive factors and longevity in a female birth cohort of 1916-17; Netherlands Cohort Study on diet and cancer (1986-2007).

entry for these analyses was restricted to the oldest birth cohorts (1916, and 1917) of the NLCS cohort, similar to a NLCS study published earlier [14]. The women from these two birth years form the longevity cohort for the current analyses.

Follow-up for vital status of the longevity cohort until the age of 90 (2006-2007) was 99.9% complete, which resulted in a study population of 4,161 women (Fig. 1). The NLCS has been approved by the institutional review boards of Maastricht University (Maastricht) and the Netherlands Organisation for Applied Scientific Research TNO (Zeist).

2.2. Exposure assessment

At baseline, participants filled in an 11-page self-administered questionnaire, including detailed information on number of childbirths (incl. stillbirths), age at first birth, age at menarche, age at menopause, induction of menopause (natural/surgical/or by medication), oral contraceptive (OC) use (incl. age at initiation and quitting age), and use of Hormone Replacement Therapy (HRT) (incl. age at initiation and quitting age). In an open question, participants could indicate whether they had undergone a surgery, by which the researchers could identify whether women had undergone oophorectomy, hysterectomy, or both. Menstrual lifespan was defined by the number of years between menarche and menopause, minus the number of full-term pregnancies x0.75 years and the duration of OC use (in years), as was done before in other analyses [6,15]. Additional baseline information was collected on lifestyle, diet, other cancer risk factors and history of diseases at baseline.

2.3. Statistical analyses

Baseline characteristic were presented by survival status at the age of 90 years. Mean values with corresponding SD were presented for continuous variables, and percentages for categorical variables. Participants (n = 1,482) with missing information on age at menarche, age at menopause, and a priori confounders were excluded from the analyses (Fig. 1).

The association between several reproductive factors and the likelihood of reaching 90 years was assessed by multivariable-adjusted Cox regression models with a fixed follow-up time [16,17]. Huber-White sandwich estimator was used to calculate standard errors to account for underdispersion [18]. A priori confounders were selected based on the literature and directed acyclic graphs (DAGs). All multivariable-adjusted models were corrected for age (years), smoking status (never, former, current), number of cigarettes smoked per day (continuous, centered), smoking duration in years (continuous, centered), alcohol consumption (0,0.1-15, > 15 g/day), educational level (primary/ lower vocational education, junior/senior high school, and higher vocational/ university), energy intake (kcal, continuous), non-occupational activity (≤ 30, > 30-60, > 60-90, > 90 min/day), and body mass index (BMI) at baseline (< 18.5,18.5-25,25- < 30,30 + kg/m2). Other potential confounders, including marital status (never married, divorced, married, widowed), history of selected diseases at baseline (0,1,2, and ≥ 3 diseases), number of childbirths (continuous), age at first birth (continuous, centered), hysterectomy/oophorectomy (yes, no), and OC use (yes, no), age at menarche (9-12,13-14,15-16, and 17-22 year), age at menopause (24-44,45-49,50-54, and 55-65 year), and hypertension (yes/no) were added to the model depending on the association under study, based on literature/DAGs and/or a 10% change-in-estimate. History of selected diseases includes heart attack, angina pectoris, stroke, any type of cancer, excluding skin cancer, and diabetes. Categorical exposures were fitted as continuous variables in trend analyses.

In earlier studies, a non-linear relationship between age at menarche, age at first birth and number of full-term pregnancies, and all-cause mortality was observed [15,19]. Therefore, we performed some additional analyses, to test for non-linear relationships. To test for non-linearity, restricted cubic spline analyses were fitted using three knots

Table 1
Baseline characteristics of the cohort members overall and by survival status in a female birth cohort of 1916-17; Netherlands Cohort Study on diet and cancer (1986-2007).

	Total	Survived to age 90	Died before age 90
n[a]	2,697	928	1,769
Age at menarche, mean ± SD	13.4 ± 1.6	13.4 ± 1.6	13.4 ± 1.6
Age at menarche, %			
9-12	29.5	29.1	29.7
13-14	49.1	48.7	49.4
15-16	17.0	17.9	16.6
17-22	4.4	4.3	4.4
Age at menopause, mean ± SD	48.4 ± 4.5	48.5 ± 4.4	48.3 ± 4.5
Age at menopause, %			
24-44	17.8	17.1	18.1
45-49	33.8	32.7	34.4
50-54	41.0	42.7	40.2
55-65	7.4	7.5	7.3
Parous, % [b]			
Yes	81.8	82.7	81.4
No	18.2	17.3	18.6
Number of children, mean ± SD [b,c]	3.6 ± 2.1	3.6 ± 2.1	3.7 ± 2.2
Number of children, % [b]			
Nulliparous	18.2	17.3	18.6
1	9.4	10.1	9.0
2	18.9	19.1	18.9
3	18.4	18.3	18.5
4	12.9	14.4	12.1
5-10	21.4	19.9	22.2
11 +	0.8	0.9	0.7
Age at first child birth, mean ± SD [b,c]	27.8 ± 4.5	28.2 ± 4.4	27.6 ± 4.6
Age at first child birth, %[b]			
Nulliparous	18.0	17.2	18.4
15-19	1.2	0.8	1.4
20-24	18.0	15.1	19.6
25-29	36.5	37.7	35.9
≥30	26.3	29.2	24.8
Hysterectomy or oophorectomy, % [b]			
Yes	11.3	11.0	11.5
No	88.7	89.0	88.5
Oral contraceptive use, % [b]			
Yes	3.7	4.2	3.4
No	96.3	95.8	96.6
Duration oral contraceptive use, mean ± SD [b,d]	3.9 ± 3.9	2.9 ± 2.4	4.5 ± 4.6
Age at first oral contraceptive use, mean ± SD [b,d]	46.7 ± 4.1	46.9 ± 3.6	46.6 ± 4.5
Hormone Replacement Therapy (HRT), % [b]			
Yes	11.4	13.3	10.5
No	88.6	86.7	89.5
Duration HRT use, mean ± SD [b,e]	4.1 ± 5.0	3.9 ± 4.7	4.3 ± 5.2
Age at first HRT use, mean ± SD [b,e]	50.2 ± 5.1	49.5 ± 4.7	50.6 ± 5.4
Menstrual lifespan (years), mean ± SD [b]	32.6 ± 5.1	32.8 ± 4.9	32.5 ± 5.1
Menstrual lifespan (years), % [b]			
< 25	8.0	7.0	8.6
25- < 30	19.5	19.2	19.7
30- < 35	37.4	37.3	37.4
35- < 40	29.2	30.5	28.5
≥40	5.9	6.0	5.8
Cigarette smoking status, %			
Never	70.9	74.9	68.7
Former	15.9	15.1	16.3
Current	13.3	10.0	15.0
BMI at baseline (kg/m^2), mean ± SD	25.1 ± 3.5	24.9 ± 3.1	25.2 ± 3.7
Non-occupational physical activity (min/day), mean ± SD	55.8 ± 48.3	56.1 ± 47.8	55.7 ± 48.5
Alcohol consumption (g/day), mean ± SD	4.9 ± 8.8	5.0 ± 8.2	4.8 ± 9.0
Energy intake (kcal/day), mean ± SD	1652 ± 371	1677 ± 374	1639 ± 368
Educational level, %			
Primary school/ lower vocational	58.2	54.9	59.9
Junior/ senior high school	33.6	35.9	32.5
University or higher vocational	8.2	9.3	7.6
Number of (selected) diseases at baseline, %			
0	72.4	82.4	67.1

(*continued on next page*)

Table 1 (*continued*)

	Total	Survived to age 90	Died before age 90
1	21.5	14.6	25.2
2	4.7	2.3	5.9
3 or more	1.4	0.8	1.8

[a] Number of participants with complete information on age at menarche, age at menopause, and confounders including: year of birth, tobacco smoking status, cigarette smoking quantity, cigarette smoking duration, educational level, alcohol consumption, BMI at baseline, non-occupational physical activity and energy intake.
[b] Number of participants used may vary from the study population due to missing values on specific exposure variables.
[c] Nulliparous women excluded.
[d] Never oral contraceptive users excluded.
[e] Never HRT users excluded.

at the 10th, 50th and 90th percentile. The model including the linear and cubic spline term was compared with the linear model using a Wald test.

Adult BMI, smoking status, and hysterectomy and/or oophorectomy are thought to potentially modify the association of age at menarche and/or menopause on the risk for all-cause mortality [7,15,20]. Therefore, we aimed to investigate whether these factors act as a potential effect-modifier in the relationship between age at menopause and/ or menarche and reaching longevity. After performing our main analyses, we observed an unexpected association between the timing of HRT use and reaching longevity. Therefore, we also investigated whether there might be effect modification by onset of menopause. Wald test and cross-product terms were used to test for effect-modification. Additional sensitivity analyses included, firstly, investigating survival to the age of 80 years instead of 90 years. Secondly, using a dichotomous age at menarche variable (< 12 vs. ≥ 12 years), as performed in Shadyab et.al [11]. Thirdly, not adjusting for disease history at baseline for the analyses between age at menopause and reaching longevity. All analyses were performed using Stata 15.0 (StataCorp. 2017. College Station, TX).

3. Results

Of the 2,697 women included in our analyses 34.4% survived to the age of 90 years. The mean ages at menarche and menopause were 13.4 year (range 9-22), and 48.4 year (range 24-65), respectively (Table 1). The percentage of women who gave birth to at least one child was 81.8%. The average number of childbirths among parous women was 3.6 (SD, 2.1), and the mean age at first birth was 27.8 years (SD, 4.5). Only 3.7% of the women had ever used OC, and among these the mean age at initiation was 46.7 years (SD, 4.1). The proportion of women who have ever used HRT was 11.4%, with an average HRT use of 4.1 years (SD,5.0). The average menstrual lifespan was 32.6 years (SD,5.1) (Table 1).

In both age-adjusted and multivariable-adjusted analyses, no significant associations were observed between age at menarche, age at menopause, and the likelihood of reaching the age of 90 years (Table 2). Nulliparous and parous women did not differ regarding likelihood of reaching longevity (RR, 0.99; 95% CI, 0.82-1.19). The number of childbirths was also not significantly associated with the likelihood of reaching longevity in the multivariable-adjusted model. In multivariable-adjusted analyses, Women who had their first childbirth at age ≥30 years were more likely (RR, 1.17; 95%CI, 0.98-1.39) to reach longevity, compared to women who had their first childbirth at age 20-24 years. No evidence for a non-linear relationship between reaching longevity and age at menarche, age at menopause, age at first childbirth, and number of childbirths with *P*-nonlinearity values of 0.794, 0.726, 0.308, and 0.614, respectively (Fig. 2). Menstrual lifespan was not associated with the likelihood of reaching longevity (Table 2).

Having undergone a hysterectomy and/or oophorectomy was not associated with the likelihood of reaching the age of 90 years, compared to women who have not undergone hysterectomy and/or oophorectomy (Table 2). Ever use of OC was not significantly associated with reaching longevity (RR, 1.16; 95%CI 0.80-1.42). A borderline significantly inverse association was observed for duration of OC use (RR, 0.92 per year; 95%CI 0.84-1.00). Ever HRT use was significantly associated with the likelihood of reaching longevity, compared to never users (RR, 1.20; 95%CI, 1.03-1.39). Among HRT users, duration of HRT use was not associated with reaching longevity. Age at HRT initiation did point towards a borderline-significant inverse association with reaching longevity (RR,0.97 per year; 95%CI 0.94-1.01) (Table 2). In additional analyses (Table 5) we observed a significantly positive association between HRT use and reaching longevity in women with an early age at menopause (< 50 years) (RR,1.32; 95% CI, 1.07-1.61), but not in women with a later age at menopause (≥50 years) (RR, 1.09; 95%CI, 0.88-1.36; *P*-interaction, 0.047).

Significant interaction by smoking status (*P*-interaction, < 0.001) and disease history (*P*-interaction, < 0.001) was observed in the relationship between age at menarche and longevity (Table 3). However, none of the comparisons showed a clear pattern or a significant association between age at menarche and longevity. Smoking status also modified the relationship between age at menopause and longevity (*P*-Interaction, < 0.001). Ever smokers with a later age at menopause (55-65 year) had a higher likelihood to reach longevity, compared to those whose age at menopause was between 50-54 years (RR, 1.72; 95%CI, 1.25-2.38). Among never smokers, the effect estimate of the same comparison pointed towards an inverse association, with a RR of 0.78 (95%CI, 0.60-1.03)(Table 3).

In analyses investigating survival to 80 years, only HRT use was significantly associated with reaching longevity (ever vs. never; RR,1.05; 95% CI, 1.00-1.11), but the strength of the association was weaker compared to our main analyses (Table 4). In sensitivity analyses, no significant association was observed between age at menarche (< 12 vs. ≥ 12 years) and reaching longevity (data not shown). When we did not adjust for disease history at baseline, the association between age at menopause and reaching longevity remained non-significant (data not shown).

4. Discussion

Using data from the Netherlands Cohort Study, no significant associations were observed between age at menarche, age at menopause, induction of menopause, parity, menstrual lifespan, and OC use in relation to the chance of reaching the age of 90 years. The age at which women had their first childbirth was borderline significantly associated with the chance of reaching longevity, where a higher age at first birth pointed towards a higher likelihood of reaching longevity. In women with an early menopause (< 50 years), ever HRT was significantly associated with a higher chance of reaching longevity, compared to never HRT-use.

Only one prospective cohort study, the Women's Health Initiative (WHI), has published on the relationship between age at menarche and

Table 2
Age- and multivariable-adjusted RRs for reaching longevity according to reproductive factors in a female birth cohort of 1916-17; Netherlands Cohort Study (1986-2007).

				Model 1[a]	Model 2[b]
	median	n	90 +	RR (95% CI)	RR (95% CI)
Age at menarche (years)					
9-12	12	796	270	0.99 (0.88-1.12)	0.99 (0.88-1.12)
13-14	13	1,325	452	Reference	Reference
15-16	15	459	166	1.06 (0.92-1.22)	1.06 (0.92-1.22)
17-22	17	117	40	1.00 (0.77-1.30)	1.04 (0.81-1.35)
P for trend				0.561	0.417
Continuous (per increment of 1 year)				1.00 (0.97-1.03)	1.00 (0.97-1.04)
Age at menopause (years) [c,d]					
24-44	42	467	154	0.91 (0.78-1.06)	0.99 (0.85-1.15)
45-49	47	889	297	0.92 (0.81-1.04)	0.95 (0.85-1.07)
50-54	51	1,067	388	Reference	Reference
55-65	55	196	68	0.95 (0.77-1.17)	0.98 (0.80-1.21)
P for trend				0.206	0.772
Continuous (per increment of 1 year)				1.01 (1.00-1.02)	1.00 (0.99-1.01)
Age at natural menopause (years) [c]					
24-44	42	399	136	0.94 (0.80-1.10)	1.01 (0.86-1.18)
45-49	47	773	257	0.91 (0.80-1.04)	0.94 (0.83-1.07)
50-54	51	973	354	Reference	Reference
55-65	55	174	62	0.98 (0.79-1.22)	1.00 (0.81-1.24)
P for trend				0.301	0.801
Continuous (per increment of 1 year)				1.01 (0.99-1.02)	1.00 (0.99-1.01)
Age at surgically induced menopause (years) [c]					
24-44	42	68	18	0.73 (0.45-1.18)	0.71 (0.44-1.16)
45-49	47	116	40	0.95 (0.66-1.38)	0.89 (0.62-1.26)
50-54	51	94	34	Reference	Reference
55-65	56	22	6	0.75 (0.36-1.57)	0.90 (0.42-1.92)
P for trend				0.459	0.250
Continuous (per increment of 1 year)				1.01 (0.98-1.05)	1.02 (0.98-1.06)
P-interaction$_{(\text{natural vs. surgical menopause})}$				0.630	0.635
Parity[e]					
Nulliparous		477	158	Reference	Reference
Parous		2,142	749	1.06 (0.92-1.21)	0.99 (0.82-1.19)
Number of children[e,f,g]					
1	1	245	92	Reference	Reference
2	2	496	173	0.93 (0.76-1.14)	0.96 (0.78-1.18)
3	3	484	168	0.92 (0.75-1.13)	0.95 (0.77-1.18)
4	4	337	129	1.02 (0.83-1.26)	1.04 (0.83-1.30)
5-10	6	559	179	0.85 (0.70-1.04)	0.88 (0.71-1.09)
11 +	12	21	8	1.01 (0.57-1.79)	1.07 (0.64-1.79)
P for trend				0.294	0.396
Continuous (per increment of 1 child)				0.98 (0.95-1.01)	0.98 (0.96-1.01)
Age at first birth (years)[e,g,h]					
15-19	19	31	7	0.78 (0.40-1.53)	0.94 (0.50-1.76)
20-24	23	468	135	Reference	Reference
25-29	27	955	343	1.25 (1.06-1.47)	1.10 (0.93-1.29)
≥30	32	688	264	1.33 (1.12-1.58)	1.17 (0.98-1.39)
P for trend				< 0.001	0.073
Continuous (per increment of 1 year)				1.00 (1.00-1.01)	1.00 (0.99-1.01)
Hysterectomy/Oophorectomy[i]					
No		2,323	811	Reference	Reference
Yes		300	98	0.94 (0.79-1.11)	0.94 (0.80-1.12)
Oral contraceptive use[j]					
Never-users		2,521	868	Reference	Reference
Ever-users		98	39	1.16 (0.90-1.48)	1.12 (0.88-1.42)
Duration oral contraceptive use[k]					
Continuous (per increment of 1 year)	3	77	32	0.91 (0.84-1.00)	0.92 (0.84-1.00)
Hormone Replacement Therapy (HRT) [j, l]					
Never-users		2,260	793	Reference	
Ever-users		295	119	1.19 (1.02-1.39)	1.20 (1.03-1.39)
Duration HRT use[k]					
< 5 years	1.5	184	73	Reference	Reference
5- < 10 years	6	32	13	1.03 (0.65-1.62)	1.24 (0.77-1.99)
10- < 15 years	12.5	16	7	1.10 (0.62-1.98)	1.13 (0.55-2.32)
> 15 years	21	10	3	0.75 (0.29-1.97)	0.67 (0.22-2.02)
P for trend				0.829	0.899
Continuous (per increment of 1 year)	3	242	96	0.99 (0.96-1.02)	0.99 (0.96-1.02)
Age at HRT initiation[k]					
< 50 years	46	95	39	Reference	Reference
≥50 years	53	152	60	0.96 (0.70-1.31)	0.95 (0.63-1.44)
Continuous (per increment of 1 year)	50	247	99	0.97 (0.95-1.00)	0.97 (0.94-1.01)
Menstrual lifespan (years)[m]					
< 25	23	209	63	0.87 (0.70-1.09)	0.96 (0.76-1.20)

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Table 2 (*continued*)

				Model 1[a]	Model 2[b]
25- < 30	28	510	174	0.99 (0.85-1.14)	1.02 (0.89-1.18)
30- < 35	33	974	337	Reference	Reference
35- < 40	37	760	275	1.05 (0.92-1.19)	1.05 (0.92-1.19)
≥40	41	153	54	1.02 (0.81-1.29)	1.06 (0.84-1.34)
P for trend				0.154	0.438
Continuous (per increment of 1 year)				1.01 (0.98-1.02)	1.00 (0.99-1.02)

[a] Age-adjusted model.
[b] Multivariable-adjusted model.
[c] Additionally adjusted for marital status, number of selected diseases at baseline, number of children, age at first birth (centered), and oral contraceptive use.
[d] Additionally adjusted for hysterectomy/oophorectomy.
[e] Additionally adjusted for age at menarche, age at menopause, marital status, number of selected diseases, hysterectomy/oophorectomy, and oral contraceptive use.
[f] Additionally adjusted for age at first child (centered).
[g] Nulliparous women excluded.
[h] Additionally adjusted for number of children.
[i] Additionally adjusted for age at menarche, number of selected diseases, number of children, age at first birth (centered), and oral contraceptive use.
[j] Additionally adjusted for marital status, number of selected diseases, age at menarche, age at menopause, number of children, age at first birth (centered), hysterectomy/oophorectomy.
[k] Never users excluded.
[l] Additionally adjusted for hypertension.
[m] Additionally adjusted for marital status, number of selected diseases, and hysterectomy/oophorectomy.

menopause, and the likelihood of reaching longevity thus far [11]. It found that a later onset of menarche (≥12 years) was associated with a significantly increased odds of reaching the age of 90 years, compared to those who had an earlier menarche (< 12 years) [11]. In our analyses, no association was observed between age at menarche and reaching the age of 90 years, also when the same comparison was made (< 12 vs. ≥ 12 years) as in Shadyab et.al. [11].(data not shown). In most studies on mortality, a later age at menarche was also found to be associated with a decreased risk for all-cause mortality [21,22]. Although most studies found a positive association between age at menarche and chances of survival, the strength of these associations was modest. One publication indicated that the age at menarche might become less important as a risk factor for survival at older ages [19]. However, in sensitivity analyses investigating survival to 80 years, we also observed no association between age at menarche and longevity (Table 4). Alternatively, early menarche has often been linked to an increased risk of diabetes and cardiovascular diseases [23,24]. In sensitivity analyses, we also observed that the relationship between age at menarche and longevity was significantly modified by history of (selected) disease status, where stronger, but non-significant, effect estimates were observed in those who had a history of disease (Table 3).

In a publication from the WHI age at menopause was positively

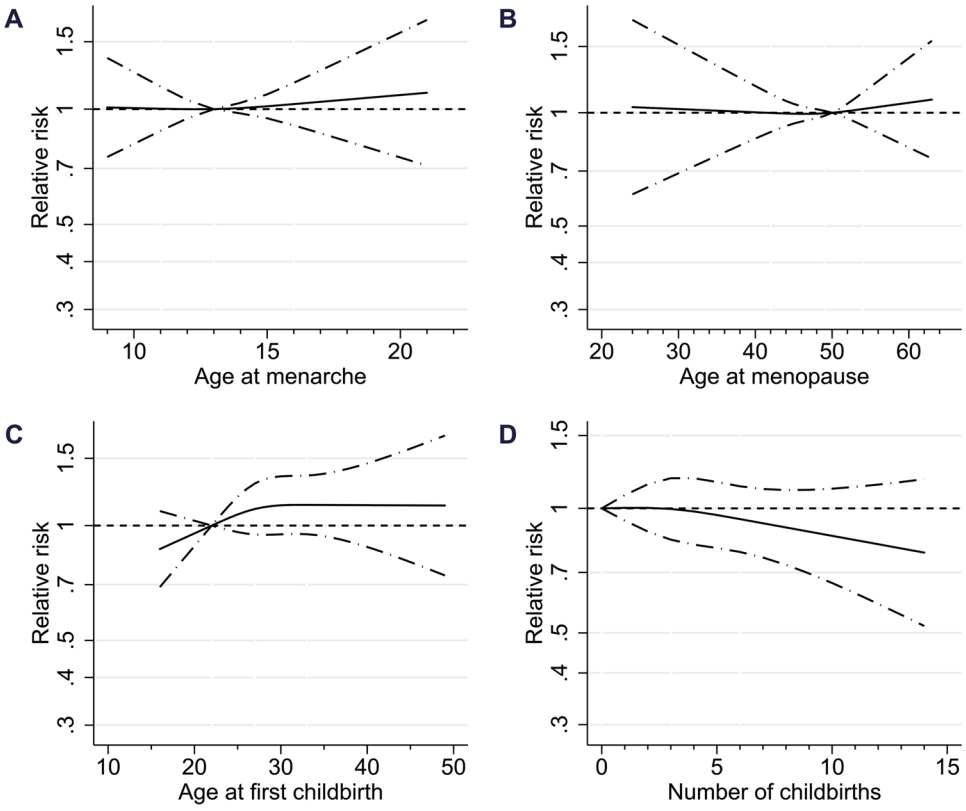

Fig. 2. Nonparametric regression curve for the association between age at menarche, age at menopause, age at first childbirth, and number of childbirths with the likelihood of reaching longevity. Solid line represents point estimate and dashed lines represent 95% confidence intervals. All models were adjusted for age, smoking status, number of cigarettes smoked per day (centered), smoking duration in years (centered), alcohol consumption, educational level, and energy intake, non-occupational activity, and BMI at baseline. **(A)** *P*-value for nonlinearity was 0.794. **(B)** Additionally adjusted for age at menarche, number of (selected) diseases at baseline, marital status, number of children, age at first birth (centered), hysterectomy/oophorectomy, and oral contraceptive use. *P*-value for nonlinearity was 0.726. **(C)** Adjusted as in B, and additionally adjusted for age at menopause. *P*-value for nonlinearity was 0.308. **(D)** Adjusted as in C, *P*-value for nonlinearity was 0.614.

Table 3
Multivariable-adjusted RRs for reaching the age of 90 years according to age at menarche, and age at menopause by strata of smoking status, BMI, and disease history in birth cohorts of 1916-17; Netherlands Cohort Study (1986-2007).

		Overall	Smoking status		Body Mass Index (kg/m2)[a]		Disease history[b]	
			Never smokers	Ever smokers	18.5- < 25	25+	No history of disease	History of disease
Age at menarche								
9-12 yr								
	90+/n	270/796	205/545	65/251	143/389	125/396	219/558	51/238
	RR (95% CI)[c]	0.99 (0.88-1.12)	1.06 (0.92-1.22)	0.80 (0.62-1.04)	0.98 (0.83-1.15)	1.02 (0.85-1.23)	0.99 (0.87-1.13)	1.10 (0.80-1.51)
13-14 yr								
	90+/n	452/1,325	339/952	113/373	260/699	186/606	381/973	71/352
	RR (95% CI)[c]	Reference	Reference	Reference	Reference	Reference	Reference	Reference
15-16 yr								
	90+/n	166/459	125/342	41/117	92/253	73/201	135/339	31/120
	RR (95% CI)[c]	1.06 (0.92-1.22)	1.04 (0.89-1.23)	1.13 (0.85-1.51)	0.98 (0.81-1.19)	1.20 (0.97-1.49)	1.02 (0.87-1.18)	1.26 (0.87-1.82)
17-22 yr								
	90+/n	40/117	26/72	14/45	25/72	15/45	30/82	10/35
	RR (95% CI)[c]	1.04 (0.81-1.35)	1.06 (0.77-1.45)	0.99 (0.63-1.56)	0.97 (0.70-1.35)	1.16 (0.76-1.77)	0.93 (0.69-1.24)	1.46 (0.85-2.52)
P-trend		0.417	0.872	0.063	0.985	0.242	0.988	0.356
P-interaction				< 0.001		0.438		< 0.001
Continuous (per increment of 1 year)								
	90+/n	928/2,697	695/1,911	233/786	520/1,413	399/1,248	765/1,952	163/745
	RR (95% CI)[c]	1.00 (0.97-1.04)	0.99 (0.95-1.03)	1.04 (0.97-1.10)	0.98 (0.94-1.03)	1.03 (0.98-1.09)	0.99 (0.95-1.02)	1.02 (0.94-1.11)
Age at menopause								
24-44 yr								
	90+/n	154/467	114/317	40/150	97/262	54/196	123/323	31/144
	RR (95% CI)[d]	0.99 (0.85-1.15)	0.97 (0.82-1.15)	1.07 (0.78-1.46)	1.06 (0.88-1.28)	0.88 (0.69-1.13)	0.99 (0.84-1.16)	0.98 (0.66-1.47)
45-49 yr								
	90+/n	297/889	222/632	75/257	162/465	133/411	243/630	54/259
	RR (95% CI)[d]	0.95 (0.85-1.07)	0.90 (0.79-1.03)	1.13 (0.88-1.45)	0.95 (0.81-1.12)	0.97 (0.81-1.16)	0.95 (0.83-1.07)	1.03 (0.74-1.44)
50-54 yr								
	90+/n	388/1,067	299/761	89/306	210/555	174/500	332/811	56/256
	RR (95% CI)[d]	Reference	Reference	Reference	Reference	Reference	Reference	Reference
55-65 yr								
	90+/n	68/196	41/143	27/53	37/96	31/99	50/133	18/63
	RR (95% CI)[d]	0.98 (0.80-1.21)	0.78 (0.60-1.03)	1.72 (1.25-2.38)	1.01 (0.77-1.33)	0.96 (0.71-1.30)	0.90 (0.72-1.14)	1.41 (0.91-2.19)
P-trend		0.772	0.854	0.302	0.783	0.446	0.983	0.368
P-interaction				< 0.001		0.684		0.524
Continuous (per increment of 1 year)								
	90+/n	907/2,619	676/1,853	231/766	506/1,378	392/1,206	748/1,897	159/722
	RR (95% CI)[d]	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.01 (0.99-1.04)	0.99 (0.98-1.01)	1.01 (0.99-1.03)	1.00 (0.99-1.01)	1.02 (0.99-1.05)

[a] Participants with a BMI < 18.5 excluded.
[b] Diseases included; heart attack, angina pectoris, stroke, any type of cancer, and diabetes.
[c] Multivariable-adjusted model.
[d] As in c, and additionally adjusted for marital status, number of selected diseases at baseline, number of children, age at first birth (centered), and oral contraceptive use.

associated with reaching longevity [11], while no associations were observed in the current study. A systematic review indicated that women who had an early menopause have an increased risk of all-cause mortality [7]. However, they concluded that the confounder sets used by the included studies varied a lot. It was noted that the strength of the effect estimate became weaker when studies adjusted for certain factors, i.e. socioeconomic status, and HRT use [7]. In stratified analyses we observed that smoking status acted as a significant effect-modifier between age at menopause and longevity, where a later menopause was associated with a decreased chance of reaching longevity in never smokers, but with an increased chance in ever smokers (Table 3). It is well-known that smoking is associated with an increased risk for premature and early menopause [25]. However, to our knowledge only one study investigated potential effect-modification by smoking when studying the relationship between age at menopause and age at death thus far [26], showing that age at menopause was not associated with age at death in never smokers, while an early age at menopause was associated with an earlier age at death in current smokers. This is in line with the results of our study [26]. It would be interesting to investigate whether these results can be replicated in other cohorts as well.

Only two studies adjusted for history of disease when studying the association between age at menopause and longevity/mortality [27,28] while other studies did not e.g. [11,21], but there was no clear difference in results between them. When we did not adjust for history of (selected) diseases the effect estimate became somewhat stronger, but not statistically significant (data not shown). Although there was no adjustment for history of disease in the main analyses by the WHI, in the discussion section it was noted that the association between age at menopause and longevity disappeared when adjusting for self-rated health [11]. In stratified analyses, it was observed that the strength of the association between age at menopause and longevity was stronger in women with a history of disease compared to those without a history of disease(Table 3). However, the Wald-test for interaction was not statistically significant. These findings, together, indicate that smoking and disease history potentially influence the relationship between age at menopause and longevity. However, it is still questionable whether they acts as confounder, effect-modifier or mediator.

In this study, no association was observed between menstrual lifespan and reaching longevity. This is in line with the result of an earlier study, investigating the relationship between menstrual lifespan and mortality [15]. In a study from the WHI [11], reproductive lifespan, defined as the age at menopause minus age at menarche, was positively associated with reaching longevity. However, in the WHI study the number of pregnancies and the duration of oral contraceptive use were not taken into account which makes these results difficult to compare.

Another possible explanation for the observed differences between

Table 4
Age- and multivariable-adjusted RRs for reaching the age of 80 years according to reproductive factors in a female birth cohort of 1916-17; Netherlands Cohort Study (1986-2007).

	median	n	80+	Model 1[a] RR (95% CI)	Model 2[b] RR (95% CI)
Age at menarche (years)					
9-12	12	796	637	0.99 (0.94-1.03)	0.98 (0.94-1.02)
13-14	13	1,325	1,076	Reference	Reference
15-16	15	459	378	1.01 (0.96-1.07)	1.01 (0.97-1.07)
17-22	17	117	91	0.96 (0.87-1.06)	0.98 (0.88-1.08)
P for trend				0.705	0.385
Continuous (per increment of 1 year)				1.00 (0.99-1.01)	1.00 (0.99-1.02)
Age at menopause (years) [c,d]					
24-44	42	467	374	0.98 (0.93-1.04)	1.02 (0.97-1.07)
45-49	47	889	711	0.98 (0.94-1.03)	1.00 (0.96-1.04)
50-54	51	1,067	869	Reference	Reference
55-65	55	196	166	1.04 (0.97-1.11)	1.05 (0.98-1.12)
P for trend				0.159	0.752
Continuous (per increment of 1 year)				1.00 (1.00-1.01)	1.00 (1.00-1.01)
Age at natural menopause (years) [c]					
24-44	42	399	323	0.99 (0.93-1.05)	1.02 (0.96-1.08)
45-49	47	773	614	0.97 (0.93-1.02)	0.98 (0.94-1.03)
50-54	51	973	797	Reference	Reference
55-65	55	174	145	1.02 (0.95-1.09)	1.03 (0.96-1.11)
P for trend				0.289	0.858
Continuous (per increment of 1 year)				1.00 (1.00-1.01)	1.00 (1.00-1.01)
Age at surgically induced menopause (years) [c]					
24-44	42	68	51	0.98 (0.82-1.17)	0.99 (0.83-1.18)
45-49	47	116	97	1.09 (0.95-1.25)	1.10 (0.97-1.26)
50-54	51	94	72	Reference	Reference
55-65	56	22	21	1.25 (1.08-1.44)	1.14 (0.96-1.36)
P for trend				0.236	0.652
Continuous (per increment of 1 year)				1.01 (1.00-1.02)	1.01 (0.99-1.02)
P-interaction$_{(\text{natural vs. surgical menopause})}$				0.039	0.093
Parity[e]					
Nulliparous		477	384	Reference	Reference
Parous		2,142	1,736	1.01 (0.96-1.06)	0.99 (0.93-1.06)
Number of children[e,f,g]					
1	1	245	200	Reference	Reference
2	2	496	409	1.01 (0.94-1.09)	1.01 (0.94-1.09)
3	3	484	394	1.00 (0.93-1.07)	1.00 (0.92-1.08)
4	4	337	272	0.99 (0.91-1.07)	0.98 (0.90-1.07)
5-10	6	559	444	0.97 (0.90-1.05)	0.97 (0.89-1.05)
11+	12	21	17	0.99 (0.80-1.23)	0.97 (0.80-1.18)
P for trend				0.248	0.171
Continuous (per increment of 1 child)				1.00 (0.99-1.01)	0.99 (0.98-1.00)
Age at first birth (years)[e,g,h]					
15-19	19	31	19	0.78 (0.58-1.03)	0.79 (0.61-1.03)
20-24	23	468	370	Reference	Reference
25-29	27	955	794	1.05 (1.00-1.11)	1.01 (0.96-1.07)
≥30	32	688	553	1.02 (0.96-1.08)	0.98 (0.92-1.04)
P for trend				0.251	0.984
Continuous (per increment of 1 year)				1.00 (1.00-1.00)	1.00 (1.00-1.00)
Hysterectomy/Oophorectomy[i]					
No		2,323	1,882	Reference	Reference
Yes		300	241	0.99 (0.93-1.05)	1.00 (0.94-1.06)
Oral contraceptive use[j]					
Never-users		2,521	2,039	Reference	Reference
Ever-users		98	81	1.02 (0.93-1.12)	1.03 (0.94-1.12)
Duration oral contraceptive use[k]					
Continuous (per increment of 1 year)	3	77		0.97 (0.94-1.01)	0.97 (0.94-1.00)
Hormone Replacement Therapy (HRT) [j, l]					
Never-users		2,260	1,812	Reference	
Ever-users		295	248	1.05 (0.99-1.11)	1.05 (1.00-1.11)
Duration HRT use[k]					
Continuous (per increment of 1 year)	3	242		1.01 (1.00-1.01)	1.00 (1.00-1.01)
Age at HRT initiation[k]					
Continuous (per increment of 1 year)	50	247		0.99 (0.98-1.00)	0.99 (0.98-1.00)
Menstrual lifespan (years)[m]					
< 25	23	209	158	0.93 (0.86-1.01)	0.96 (0.89-1.04)
25- < 30	28	510	409	0.99 (0.94-1.04)	1.00 (0.95-1.05)

(*continued on next page*)

Table 4 (*continued*)

	median	n	80+	Model 1[a] RR (95% CI)	Model 2[b] RR (95% CI)
30- < 35	33	974	789	Reference	Reference
35- < 40	37	760	628	1.02 (0.98-1.07)	1.02 (0.97-1.06)
≥40	41	153	127	1.02 (0.95-1.11)	1.03 (0.95-1.11)
P for trend				0.030	0.155
Continuous (per increment of 1 year)				1.00 (1.00-1.01)	1.00 (1.00-1.01)

a Age-adjusted model. b Multivariable-adjusted model. c Additionally adjusted for marital status, number of selected diseases at baseline, number of children, age at first birth (centered), and oral contraceptive use. d Additionally adjusted for hysterectomy/oophorectomy e Additionally adjusted for age at menarche, age at menopause, marital status, number of selected diseases, hysterectomy/oophorectomy, and oral contraceptive use. f Additionally adjusted for age at first child (centered). g Nulliparous women excluded. h Additionally adjusted for number of children. i Additionally adjusted for age at menarche, number of selected diseases, number of children, age at first birth (centered), and oral contraceptive use. j Additionally adjusted for marital status, number of selected diseases, age at menarche, age at menopause, number of children, age at first birth (centered), hysterectomy/oophorectomy. k Never users excluded. l Additionally adjusted for hypertension. m Additonally adjusted for marital status, number of selected diseases, and hysterectomy/oophorectomy.

Table 5
Ever use of Hormone Replacement Therapy and reaching the age of 90 years by onset of menopause, with corresponding test for interaction, in a female birth cohort of 1916-17; Netherlands Cohort Study (1986-2007).

	Overall	Age at menopause	
		< 50 years	≥50 years
Hormone Replacement Therapy use			
No			
90+/n	763/2,260	377/1,161	386/1,099
RR (95% CI)[a]	Reference	Reference	Reference
Yes			
90+/n	119/295	64/158	55/137
RR (95% CI)[a]	1.20 (1.03-1.39)	1.32 (1.07-1.61)	1.09 (0.88-1.36)
P-interaction			0.047

[a] Multivariable-adjusted model additionally adjusted for age at menarche, number of selected diseases, number of children, age at first birth (centered), oral contraceptive use, and history of hypertension.

the WHI cohort and NLCS cohort is the use of a different statistical method. In the analyses by Shadyab et.al., logistic regression analyses were used to calculate ORs of reaching longevity [29]. However, when the outcome is not rare, as in this case, the use of OR can easily overestimate the effect compared to RR. As a result, the higher odds of reaching longevity observed in their study might possibly be caused by this effect. Additionally, the WHI is a multi-ethnic cohort [11], while the NLCS cohort consisted primarily of Caucasian women, which might have also led to different results. Similar to the analyses by the WHI, we observed a positive association between age at first childbirth and reaching longevity [12]. In two recent prospective cohort studies similar results were observed, where a later age at first childbirth was associated with a decreased risk for all-cause mortality [15,30]. However, one should realize that all women in our cohort did survive childbirth. Surviving childbirth at an older age might be an indicator of good overall health, which might have influenced our results. Consequently, we would not advice to delay childbirth giving the increased risk for obstetric complications, and other negative consequences known to be associated with a later age at childbirth as well [31].

Parity and number of childbirths were found to be positively associated with reaching longevity [12], and inversely associated with all-cause mortality in several studies e.g. [15,32]. In our analyses, ever parous and an increased number of childbirths were not associated with an increased likelihood of reaching longevity. A possible explanation for this difference might lie in the era from which the women in our analyses stem. Around 1900, having multiple childbirths has been hypothesized to be a commonly used strategy to increase the chance of surviving offspring, because childhood mortality was more prevalent [33]. With a decreasing risk of childhood mortality in the early 20th century, the average number of childbirths also decreased. The generation used for these analyses grew up in a period in which these strategies were changing [33]. Hypothetically, the choice of having multiple children in that time could still have been more common in socioeconomically vulnerable families, as suggested by earlier studies [34]. Because these women might stem from a more vulnerable socioeconomic background, their own likelihood of reaching an old age might have also been smaller. Unfortunately, information on socioeconomic vulnerability is not available in our cohort. Although most studies observed a beneficial effect of increased childbirths e.g. [12,15,30], the underlying strategies used in this time period might have counterbalanced the effect of these two conflicting effects on longevity. However, this suggestion is speculative and should be better explored in future studies.

Although there are no studies that have assessed the relationship of OC use with longevity yet, several studies have investigated the relation to all-cause mortality, and found no, or only a weak protective association between OC-use and mortality e.g. [10,35]. In our study we also observed no significant association between OC-use and reaching longevity, but the number of ever OC users was small (Table 2). We did observed a significantly inverse association between the duration of OC use and the likelihood of reaching longevity among ever users. However, because the women in our cohort were already above the age of 45 years when oral contraceptives were introduced in the Netherlands, these findings may not be representative for typical OC users nowadays.

A large systematic review based on 32 randomized controlled trials indicated that there is no association between the use of HRT and mortality risk [9]. In cohort studies, the use of HRT has been inversely associated with all-cause mortality on the short-term (< 5 years) e.g. [36], but not on the long-term (≥5 years) [8,36]. In the current study, HRT use was significantly positively associated with reaching longevity, compared to never users. The age at HRT initiation was inversely associated with reaching longevity. This observation raised the hypothesis that the use of HRT might be more beneficial for those who had an early menopause in terms of reaching longevity, which we therefore decided to further investigate. In these additional analyses we indeed observed a significantly positive association between ever HRT use and reaching longevity, but this was limited to women who had an early menopause (< 50 years of age)(Table 5).

Strengths of the study are the prospective study design which limits the risk for information bias and selection bias, the large sample size, and detailed information on the main exposures, as well on potential confounders. Furthermore, our study population was very homogeneous with respect to age, making confounding by age unlikely.

There were some limitations to our study. The women included in these analyses already survived to an advanced age (68-70 years). Reproductive factors might have played a role in premature mortality before the age of 69 years, but these women were not included in the analyses. This might have led to survivorship bias. Furthermore, only limited information was available on the socioeconomic circumstances

of these women. Although we had data on educational level of these women, there is still a possibility of residual confounding by socio-economic status on a household level, which might have influenced our results.

In conclusion, timing of menarche and menopause were not associated with the likelihood of reaching the age of 90 years. However, we did observe that these relationships were significantly modified by smoking status and disease history. Parity and the number of children were also not related to the likelihood of reaching longevity. Age at first childbirth did show a positive association with the likelihood of reaching the age of 90 years. Ever HRT use also showed a significantly positive association with reaching longevity, but in additional sensitivity analyses we observed that this was only the case in women who had an early age at menopause (< 50 years).

Contributors

Lloyd Brandts analyzed the data, prepared the tables and drafted the manuscript.

Frans W.A. van Poppel provided critical revisions for important intellectual content.

Piet A. van den Brandt designed the study, coordinated the data collection and analyses, and provided critical revisions for important intellectual content.

All authors conceptualized the paper, and read and approved the final version of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical approval

The NLCS has been approved by the institutional review boards of Maastricht University (Maastricht) and the Netherlands Organisation for Applied Scientific Research TNO (Zeist).

Provenance and peer review

This article has undergone peer review.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. The informed consent does not allow for data to be shared.

CRediT authorship contribution statement

Lloyd Brandts: Conceptualization, Formal analysis, Methodology, Visualization, Writing - original draft, Writing - review & editing. **Frans W.A. van Poppel:** Conceptualization, Writing - review & editing. **Piet A. van den Brandt:** Conceptualization, Data curation, Methodology, Investigation, Project administration, Supervision, Writing - review & editing.

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