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The Healthy Aging Index analyzed over 15 years in the general population: The Doetinchem Cohort Study

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ABSTRACT

The Healthy Aging Index (HAI), an index of physiological aging, has been demonstrated to predicts mortality, morbidity and disability. We studied the longitudinal development of the HAI to identify aging trajectories and evaluated the role of baseline sociodemographic characteristics and lifestyle factors of the trajectories. Four measurements with intervals of 5 years were included from the Doetinchem Cohort Study. The HAI reflects levels of systolic blood pressure, non-fasting plasma glucose levels, global cognitive functioning, plasma creatinine levels and lung functioning. The HAI score ranges from 0 to 10: higher scores indicate a better health profile. Latent class mixture modelling was used to model within-person change and to identify aging trajectories. Area under the curve was calculated per trajectory to estimate total healthy years. In total, 2324 women and 2013 men were included. One HAI trajectory was identified for women, and two trajectories for men, labelled '*gradual*' aging (76%) and '*early*' aging (24%). Men who were medium/high educated, below 36 years at baseline, complied with guidelines on physical activity and were not obese in any round were associated with increased odds to '*gradual*' aging of 1.46 (CI: 1.18–1.81), 1.93 (CI: 1.42–2.62), 1.26 (1.02–1.57) and 1.76 (1.32–2.35), respectively. Between 30 and 70 years of age, men in the '*early*' aging trajectory had the least healthy years (29.6 years), followed by women (30.1 years), and '*gradual*' aging men (34.7 years). This study emphasizes that 'physiological aging' is not only an issue of older ages. Between 30 and 70 years of age, '*early*' aging men and women had approximately five healthy years less compared to '*gradual*' aging men. Lifestyle factors (e.g. nutrition and physical activity) seem to play an important role in optimal aging.

1. Introduction

Life expectancy continues to rise worldwide so there is an increasing interest in how aging affects health. Because health comprises a wide variety of factors, measuring the effects of aging on health is challenging (Rowe and Kahn, 1997). Current aging indices use a range of factors related to health and are based on, for instance, comorbidity (Charlson et al., 1987; Quan et al., 2011), frailty (Dent et al., 2016) or physiological parameters (Sanders et al., 2012). One example of an aging index based on physiological parameters only is the Healthy Aging Index (HAI) (Sanders et al., 2014).

The HAI is an adaptation of the "Physiologic Index of Comorbidity" (PIC) that was developed by Newman, Boudreau (Newman et al., 2008), which included measurements of carotid intima-media thickness, pulmonary vital capacity, serum cystatin-C, white matter grade, and serum fasting glucose. The PIC was sensitive to detect subclinical disease in older adults (Newman et al., 2008), but the indicators used for this index are not widely available in epidemiological studies, which limits its wider application (Sanders et al., 2014). The HAI was shown to be a reliable adaptation of the PIC, as it predicts mortality independently of chronological age and comorbidities (Sanders et al., 2012; Sanders et al., 2014; McCabe et al., 2016; Wu et al., 2017). In addition, it was shown that the HAI is associated with the risk of incident disability, mobility limitations, slow gait speed and incident

Abbreviations: AUC, area under the curve; DCS, Doetinchem cohort study; FVC, Forced Vital Capacity; HAI, Healthy Aging Index; LCMM, latent class mixture modelling; PIC, Physiologic Index of Comorbidity; RBG, random blood glucose; SBP, systolic blood pressure

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Table 1
Cut-off off points used to categorize each indicator of the HAI.

Healthy Aging Index indicators								
Score for group	SBP, mmHg	RBG, mmol/L	Creatinine, mmol/L		FVC, L		Cognition, *Z*-score	
			Men	Women	Men	Women	Men	Women
0 = least healthy	≥143	≥11.1	≥ 114.9	≥88.4	< 3.2	< 2.1	< 10th percentile in T4	< 10th percentile in T4
1 = intermediate	126–143	5.6–11.1	97.2–114.9	70.7–88.4	3.2–3.8	2.1–2.6	10th percentile – 0 in T4	10th percentile – 0 in T4
2 = healthiest	< 126	< 5.6	< 97.2	< 70.7	≥3.8	≥2.6	> 0	> 0

cardiovascular disease (Sanders et al., 2012; McCabe et al., 2016; Rosso et al., 2014).

The HAI involves indicators for five physiologic systems that indicate both clinical and sub-clinical changes in organ structure and function (Sanders et al., 2012). Blood pressure, glucose, creatinine, lung function and cognitive functioning are used as parameters in the HAI. Due to supporting evidence, partly discussed above, the HAI is increasingly being used as a summary measure of physiological health. In addition to chronological age, these biomarkers can be used to predict future events (Kemper et al., 2000). Thus, a biomarker based index may help to identify people who have the potential to remain healthy throughout their life course.

It is important to understand heterogeneity in health trajectories related to aging in order to understand how and why people age in the way they do. Gaining insights in the dynamics of the effect of age on health can be achieved by examining how the HAI develops over the life course in a population. Some studies have analyzed the relation between aging indices similar to the HAI with age. Studies in samples of older (50+) and elderly (70+) people (Wilkie et al., 2013; O'Connell et al., 2018; Tampubolon, 2016) suggest that there is a sex difference in aging trajectories and that baseline HAI scores is of importance for the subsequent aging trajectory. The follow-up time in previous studies was maximum 10 years with repeated measurements up to a number of 3. To gain more insight into physiological aging over the life course, longitudinal studies with more measurements, longer follow-up time, and covering a longer span of the adult life course are desired.

In this study we used four measurement points from the Doetinchem Cohort Study (DCS) (Picavet et al., 2017), spanning a period of 15 years, to study development in individual HAI scores over the life course among people aged between 30 and 70 years in the Netherlands. The objective of this study was to describe the development of the HAI with age for men and women separately, and to investigate whether different typical aging trajectories could be identified in the data. For the different trajectories, the number of years lived in full health was calculated and the role of baseline sociodemographic characteristics and lifestyle factors were evaluated.

2. Methods

2.1. Setting and participants

Between 1987 and 1991, a total number of 20,155 inhabitants (aged 20–59 years) of the city of Doetinchem, the Netherlands were invited to participate in the study named "Monitoring Project on Cardiovascular Disease Risk Factors", based on a random selection stratified by sex and age (Verschuren et al., 2008). The response rate was 62% (n = 12,405). From this group, 7769 people were randomly selected and invited for the second examination (1993–1997) and future follow-up examinations in the DCS. Supplementary file S1 provides an overview of the response of follow up measurements thus far. The study is approved by the Medical Ethics Committees of the Netherlands Organization of Applied Scientific Research and the University of Utrecht. The cohort profile is described in detail elsewhere (Picavet et al., 2017). Not all HAI indicators were measured in round 1 of the DCS. Therefore, we used the data from round 2 (1993–1997) as baseline (T1) until round 5 (2008–2012) (T4) for the current study. Participants were included in the study if they had at least one complete HAI score (e.g. values on all the five indicators of the HAI) in the four included measurements. In total 2324 women and 2013 men were included.

2.2. Construction of the Healthy Aging Index

The HAI used in this study is based on the study of Sanders et al. (2012) and involves five indicators. Indicators were each graded at one of the three levels, with a score of 0 meaning the 'least healthy' outcome, a score of 1 an 'intermediate' outcome and a score of 2 the 'healthiest' outcome. Then, the HAI score was calculated by adding up all the five indicator scores. Thus, HAI scores can theoretically range between 0 and 10, with 0 indicating the least healthy and 10 the healthiest score. Cut-off points, see Table 1, were replicated from previous studies for systolic blood pressure (SBP), creatinine and forced vital capacity (FVC) (Sanders et al., 2012; Sanders et al., 2014; McCabe et al., 2016). Clinical cut-off points were applied for random blood glucose (RBG) and cognitive function (Ceriello and Colagiuri, 2008) Bowen, Xuan (Bowen et al., 2015). Nooyens et al. (2011) have described the cognitive tests in more detail. Cognition scores were transformed into z-scores to capture the decline rate over time (Nooyens et al., 2008; Nooyens et al., 2010). Supplementary file S2 provides further information about the way measurements were conducted.

2.3. Baseline sociodemographic characteristics and lifestyle factors

Information on several sociodemographic characteristics and lifestyle factors were collected by an interviewer or via postal survey. Age at baseline was dichotomized as ≥36 years and younger in order to account for a potential cohort effect. Educational level was dichotomized into low (intermediate secondary education or less) and medium/high (intermediate vocational, higher secondary education, higher vocational education or university). Work status was defined as having a formal paid job (including salaried employment and self-employed) or being unemployed. Marital status was dichotomized, being married also included registered partnership. Lifestyle was defined by the following variables: sleep, physical activity, body mass index (weight and height were assessed by a health care worker (weight (kg)/[height (m)]^2)), smoking status and alcohol consumption.

2.4. Statistical analyses

The HAI scores were interpreted as observed representations of a latent aging process. Link functions were used to map the latent aging process (that is assumed to be Gaussian) to these observations (like in generalized linear models (McCullagh, 1989)). We expected that the population consists of a number of latent classes representing different aging trajectories. Each latent class has its own mean profile that was modelled according to age. The approach of latent class mixed models (LCMM) (Proust et al., 2006; Proust-Lima et al., 2017) offers a unified framework and estimation process for these models. For a predefined

number of latent classes, the mean class-profiles were modelled using linear mixed models on the latent scale, with a random intercept per individual. Two types of link functions were examined to map the latent scale onto the observed HAI scores: a linear transformation and a threshold function. The mean class profiles were modelled as a smooth function of age, by means of natural cubic splines with different degrees of freedom (), defining the overall smoothness. Among the different fitted models, the model with the smallest Bayesian Information Criterion (BIC) was chosen as the best model (Schwarz, 1978), where the maximum likelihood was penalized for the number of parameters used to fit the model. All analyses were performed in R 3.5.2 (Team, 2019) with the package lcmm version 1.8.1 (Proust-Lima et al., 2019).

The number of healthy life years per trajectory was calculated by means of the area under the curve (AUC) between the ages of 30 and 70, analogous to the concept of Quality-Adjusted Life Years (QALYs), with the mean HAI score for the trajectory as a quality of life weight attached to each year. Thus, a year lived with a HAI score of 10 equals a year in full health, and receives a score of 1, whereas a year lived with a HAI score of 8 receives a score of 0.8. Scores for all years between 30 and 70 years of age are then aggregated to compute the number of healthy life years for the trajectory.

Lastly, regression analyses were conducted to investigate which baseline sociodemographic characteristics were associated with the identified latent classes. We accounted for the time sensitivity of the lifestyle variables by creating dummies that reflected the duration of engagement in each behavior. Supplementary file S3 provides detailed information about the dichotomizations. We investigated several forms of dummy variables (e.g. always, sometimes, never) to investigate how these mechanisms were associated with the identified trajectories and presented the most informative models.

2.5. Missing values

For each of the five indicators of the HAI, participants with missing values on two or more of the four measurements were disregarded. Data for participants with less than two missing values on an indicator were manually imputed based on values from other measurements. For SBP, RBG, creatinine and FVC we took the average value of the measurement before and after the missing data point. In case the first measurement was missing, we used the baseline values of the DCS. When this value was also missing, the value of round 3 (T2) was duplicated. In case the last SBP measurement was missing, we replicated the value at T3 for imputation. Missing data for global cognition functioning were imputed based on the assumption that global cognitive functioning will not recover after a decrease has started (Rietman et al., 2019). Therefore, in case of missing values, the value of a consecutive round was used for imputation. As cognitive tests were only performed among participants aged 45 years or older, we assumed that participants younger than 45 years were cognitively healthy (Rietman et al., 2019). We compared the imputed sample with the non-imputed sample to ensure that the values and population characteristics did not differ considerably (also see Supplementary files S4–S9).

3. Results

3.1. Sample characteristics

Table 2 presents the baseline (T1) sociodemographic characteristics, lifestyle characteristics and HAI values of the study sample. With a response rate of 71% the study sample consisted of 2324 women and 2013 men, aged 25–65 years at baseline (T1). Men were significantly older, had a higher education and were more often employed. Supplementary file S10 shows the characteristics of the total sample at T1. The study sample was slightly younger and consequently had somewhat healthier values for the HAI indicators.

Table 2
Characteristics of Doetinchem Cohort respondents, study sample at T1.

Socio-demographic characteristics	Study sample (n = 4337)	
	Women, n = 2324 (54%) %	Men, n = 2013 (46%) %
Mean age (SD)*	42.8 (10.0)	43.7 (10.0)
Age categories, %		
26–35 yr	24.2	21.4
36–45 yr	42.0	41.4
46–55 yr	18.3	20.0
56–65 yr	15.5	17.2
Educational level, %*		
Low	59.4	44.0
Medium	25.5	32.4
High	15.1	23.6
Paid employed (yes)*	48.9	80.0
Marital status (married)	81.8	80.1
Sleep (< 7 h per night)*	11.8	18.8
Smoke status*		
Smoker	31.7	34.1
Ex-smoker	32.5	36.9
Never smoker	35.9	29.0
Physical activity (compliance with guideline)	78.6	76.1
BMI (kg/m^2), mean (SD)*	25.3 (4.1)	25.9 (3.1)
Healthy Aging Index indicators	μ (SD)	μ (SD)
Systolic blood pressure, mmHg*	119.3 (15.8)	127.0 (14.9)
Random glucose, mmol/L*	5.2 (1.5)	5.4 (1.3)
Creatinine, mmol/L	72.7 (12.7)	72.5 (12)
Forced Vital Capacity (FVC), L*	4.0 (0.6)	5.4 (1.1)
Global cognitive function, z-score[a]	0.03 (0.7)	0.05 (0.8)
Healthy Aging Index*	8.3 (1.5)	8.5 (1.4)

* Significant at $p < 0.05$ level derived from chi^2 and t-tests.
[a] Scores of T2 are presented due to small sample size at T1.

3.2. Healthy Aging Index – descriptions

The distributions of the HAI scores for the included men and women in the different measurement rounds are presented in Fig. 1. At T1 the study population was aged between 25 and 65 years, at T4 between 40 and 80 years. In the first measurement, at T1, the HAI scores showed a skewed distribution towards the healthy end of the spectrum, with average values of 8.5 and 8.3 for men and women respectively. Fifteen years later, at T4, there was a shift in the distribution of the HAI scores towards the unhealthy end of the spectrum (nearing a normal distribution). Only 11% of the men and 8% of the women had a HAI score of 10, with average scores of 7.2 and 6.9.

The average population lines for the HAI scores by age stratified by gender can be found in Supplementary file S11. At age 30, women had an average HAI score of 8.9, while men had a slightly higher score of 9.3. The onset of decline in the HAI scores started for both men and women around the age of 40 years. Women had a 1.5 lower HAI score at the age of 70 compared to men (7.0 versus 5.5).

3.3. Healthy Aging Index – latent class mixture modelling

The latent class mixed models revealed two distinct HAI trajectories for men and one for women (Fig. 2). For men, trajectory 1 included 24% (n = 492) of the participants and this group was characterized by a relatively early start of decline in HAI score while it flattens later on. Accordingly, the men following this trajectory were named '*early*' aging men. The mean HAI score for '*early*' aging *men* was 9.0 at age 30, 8.4 at age 40, 7.1 at age 50 and 6.3 at ages 60 and 70. The remaining men (76%) followed a different trajectory, with on average a more gradual and consistent decline that started later with an average HAI score of 9.4 at ages 30 and 40, 8.8 at age 50, 8.2 at age 60 and 7.2 at age 70. The men following this trajectory were consequently named '*gradual*' aging

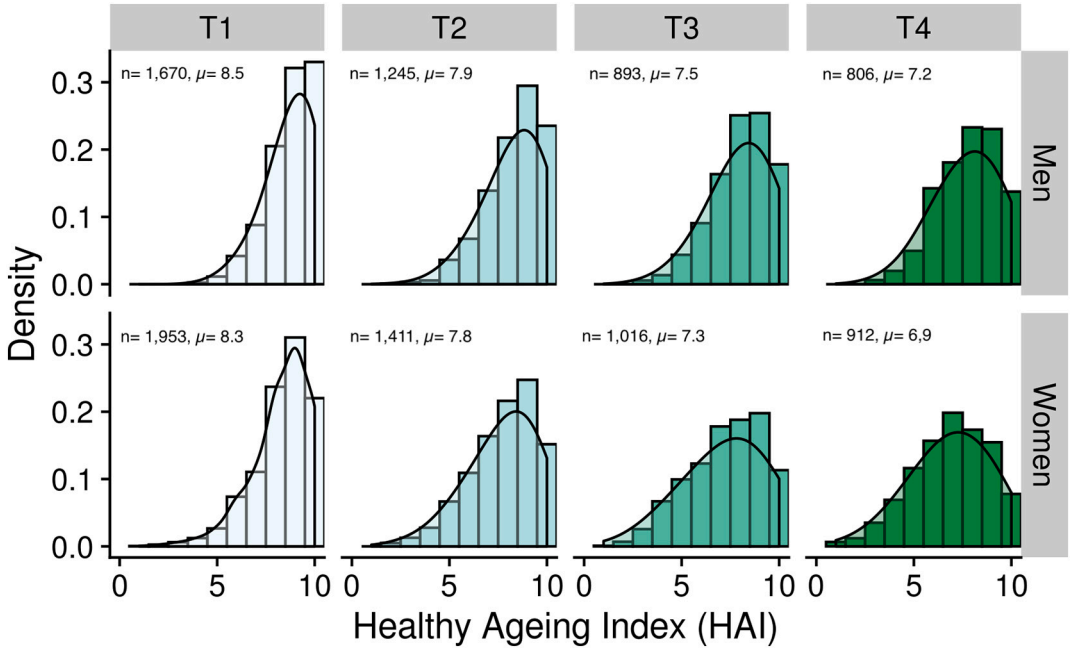

Fig. 1. Distribution of the HAI scores at four different time points.

men. The area under the curve (AUC), as calculated for the trajectories between the ages of 30 and 70 years, was on average 29.6 for the '*early*' aging men and 34.6 for the '*gradual*' aging men. For women, only one latent trajectory emerged in the data. From the age of 40 years onwards, this trajectory showed a decline of 1.0 HAI score unit every 10 years which resulted in a score of 5.5 at age 70 and an AUC of 30.1, which is comparable to the AUC of the '*early*' aging men trajectory. Put differently, of the potential 40 years in full health lived between the ages 30 and 70, '*gradual*' aging men on average lived 34.6 healthy years, while women and '*early*' aging men lost about 10 years (i.e. lost about five healthy years more than '*gradual*' aging men).

Looking at the three identified trajectories together (Fig. 3), it becomes clear that the '*early*' aging men started with the steepest decline. However, this decline flattened around the age of 60 years while the decline for women continued. Consequently, women on average end with the lowest HAI score at age 70. The '*gradual*' aging men show the most favorable HAI trajectory.

3.4. Characteristics of the aging trajectories

At baseline, the '*gradual*' aging men were slightly, though significantly, younger (average 43.4 years) and were higher educated than the '*early*' aging men (average 44.9 years). The trajectories did not differ significantly in employment or marital status.

Table 3 shows the Odds Ratios (ORs) of trajectory membership for men by baseline sociodemographic characteristics and engagement in

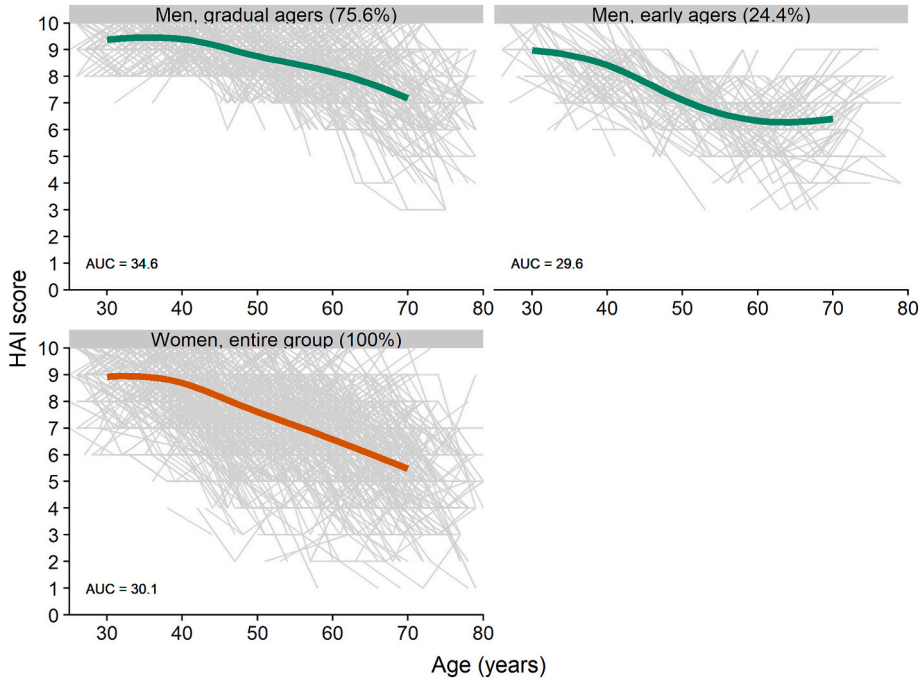

Fig. 2. Identified trajectories of the HAI for men and women.

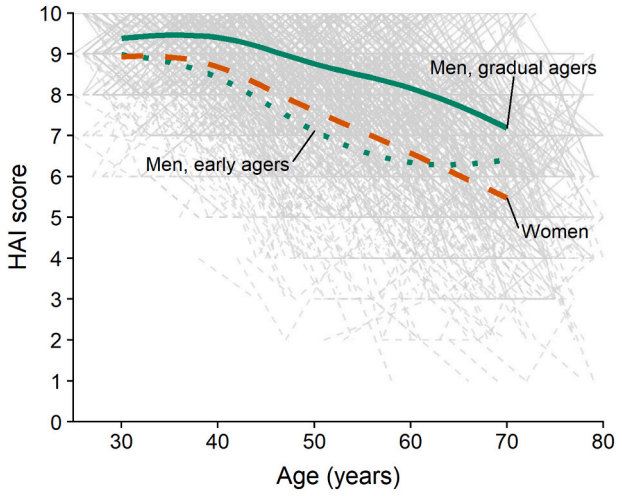

Fig. 3. Identified trajectories of the HAI for men and women pictured together.

lifestyle behaviors over the four measurement rounds. Being aged below 36 years at baseline and having a medium or high level of education (versus low) were associated with increased odds of belonging to the '*gradual*' aging men. Regarding lifestyle behaviors, compliance with the Dutch guideline for physical activity in all measurement rounds showed increased odds of belonging to the '*gradual*' aging men (model 3). However, this association became no longer statistically significant after the addition of other lifestyle variables in the model (model 6). Not being obese in any measurement round showed increased odds of belonging to the '*gradual*' aging men (model 4) and the association remained statistically significant in the model with all investigated lifestyle variables included (model 7). The association in the exact opposite direction also holds: being obese in every measurement round made it less likely to be in the '*gradual*' aging trajectory. Surprisingly, the odds of belonging to the '*gradual*' aging men were not statistically significantly altered with smoking status and alcohol consumption (model 5, model 6, model 7).

95% confidence intervals in parentheses.

4. Discussion

This study emphasized that 'physiological aging' is not only an issue of older age, but that a much larger part of the life course is relevant in addressing physiological aging related research questions. Using the HAI, we identified two distinct aging trajectories among men and only one among women. The two trajectories among men were described as '*gradual*' aging (75% of the men) and '*early*' aging (25% of the men). The AUC estimates revealed that of the potential 40 years in full health (age range 30–70), '*early*' aging men lost, on average, the most years in full health (10.4 years), followed by women (9.9 years), and '*gradual*' aging men (5.4 years). This was the first study that investigated HAI trajectories with four time points, covering a period of 15 years.

Two other studies have investigated the HAI (or a similar index) with multiple measurements over time. O'Connell, Marron (O'Connell et al., 2018) found a decrease in the HAI of at least 1.0 point over a period of nine years among an older population (average age of 74 years at baseline). We modelled trajectories within the age range of 30 and 70 years, and found a decrease in HAI score of 1.0 point between the ages of 60 and 70 years for '*gradual*' aging men, whereas '*early*' aging men had a stable score over this same age range. Tampubolon (Tampubolon, 2016) studied a very similar index over a period of nine years among people aged 50 years and older. They found a sharper decline for women than for men, while women had a more favorable score at baseline. The distribution of the index score was also wider for women than for men. These results are in line with our findings. Previously it has been suggested that sex differences may be explained by the biological variation between men and women, such as differences in hormones and the prevalence of metabolic syndrome (Yang and Kozloski, 2011). This finding is in agreement with the 'sex paradox', i.e.

Table 3
Odds ratio's for the two identified HAI trajectories for men.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
	Odds ratio	Odds ratio	Odds ratio	Odds ratio	Odds ratio	Odds ratio	Odds ratio
	Gradual agers (reference group: early agers)						
Sociodemographic variables							
< 36 years at baseline	1.93	1.93	1.96	1.92	1.95	1.93	1.91
(reference: ≥36 years)	(1.42–2.62)	(1.42–2.62)	(1.45–2.67)	(1.41–2.61)	(1.44–2.66)	(1.42–2.62)	(1.40–2.60)
Medium & high educated (reference: low)	1.47	1.47	1.45	1.34	1.43	1.45	1.36
	(1.18–1.81)	(1.19–1.82)	(1.17–1.80)	(1.07–1.66)	(1.15–1.77)	(1.17–1.79)	(1.09–1.69)
Married (reference: not married)	1.09	1.09	1.06	1.03	1.07	1.09	1.03
	(0.82–1.43)	(0.82–1.44)	(0.80–1.40)	(0.77–1.37	(0.81–1.42)	(0.82–1.44)	(0.78–1.37)
Paid employed (reference: not employed)	0.92	0.92	0.90	0.86	0.91	0.90	0.86
	(0.71–1.20)	(0.70–1.20)	(0.69–1.18)	(0.65–1.22)	(0.69–1.18)	(0.94–1.46)	(0.66–1.13)
Time sensitive lifestyle variables							
> 7 h sleep in all rounds (reference: ≤7 h)		0.97					0.93
		(0.78–1.22)					(0.74–1.16)
Sufficient physical activity in all rounds (reference: the rest)			1.26				1.08
			(1.02–1.57)				(0.85–1.37)
Not obese in all rounds (reference: the rest)				1.69			1.76
				(1.27–2.00)			(1.32–2.35)
Obese in all rounds (reference: the rest)				0.56			0.57
				(0.38–0.81)			(0.39–0.83)
Non-smoker in all rounds (reference: the rest)					1.19		0.88
					(0.96–1.48)		(0.67–1.16)
Alcohol consumer in all rounds (reference: the rest)						1.18	0.89
						(0.95–1.46)	(0.69–1.16)
Constant	2.24	2.28	2.12	2.19	2.16	2.15	2.33
	(1.61–3.11)	(1.59–3.27)	(1.52–2.96)	(1.55–3.09)	(1.55–3.01)	(1.54–3.00)	(1.60–3.41)
Nagelkerke R^2	0.018	0.018	0.020	0.032	0.019	0.019	0.034
McFadden R^2	0.016	0.016	0.019	0.029	0.018	0.017	0.031

the finding that women live longer than men, but tend to have worse health (Nathanson, 1975). In our study population, men on average had a higher level of education than women, which suggests that more women in the sample had a socio-economic disadvantage for healthy aging. Since people with different educational levels tend to have different possibilities and lifestyles, and thus belong to a different study population, this might be a reason why we found two trajectories in men but only one in women.

On average, the male respondents in the two trajectories differed 1,5 years by age. We studied the change of the HAI while aging, with a method that assumes no differences between generations or birth cohorts. The regression analysis confirms a difference in age between the two trajectories, but also shows that other factors are significantly associated when there is controlled for age.

The regression analysis for the aging-trajectories among men showed associations with baseline educational level and age; and time-variant physical activity and BMI. The well-known social gradient in health outcomes (Marmot, 2005) also seems to be present when biomarkers are used as health status indicators. Adherence to the Dutch physical activity guidelines, and not being obese increased the chance to follow the '*gradual*' aging trajectory. Physical activity has been widely shown to benefit the aging process in a variety of domains, ranging from better social outcomes to a reduced risk for chronic diseases (Bauman et al., 2016). It has been suggested that "obesity disables, and smoking kills" (Reuser et al., 2009). Indeed, we found that being obese was associated with membership in the early aging trajectory. However, smoking status was not associated with one of the identified trajectories. The proportion of those who smoked was not significantly different between the total sample and our study sample, nor between the identified trajectories. Hence, a selective drop-out among smokers is unlikely. We found no other plausible explanations for this finding. In this study, alcohol consumption was also not associated with the aging trajectories. However, the data did not allow us to stratify between moderate and excessive alcohol consumption, which may explain this finding. The behaviors included in the models are sensitive to change over time (e.g. someone may start or quit smoking). We took this into account by the inclusion of dummy variables that reflected the different measurement rounds. Additional research is needed to study time-variant independent and dependent variables to gain insights in the relationship between a changing lifestyle while aging.

Two aspects are important to consider when interpreting the HAI change over time. First, the magnitude of change may be associated with the initial HAI score since participants starting with a disadvantaged score have less to lose. O'Connell, Marron (O'Connell et al., 2018) adjusted for the initial score to account for this impact, although they studied an already older population. In our study, trajectories had comparable HAI scores at age 30, ranging between 8.9 and 9.4 and thus differences in trajectories are unlikely to be due to these values. Second, the meaning of a change in HAI score is related to the current HAI score. Similar reductions in HAI scores in different trajectories are likely to have different effects on the (experienced) health state. People who experience a reduction in HAI score, but have a relative high HAI score, may be expected to have more reserve (e.g. they are "healthier" as defined by the HAI) compared to people with a lower HAI score. Similarly, it may matter what elements constituted the decrease in HAI scores.

4.1. Limitations and strengths

First, as in most prospective cohort studies, selective attrition is an obstacle in the interpretation of the results: healthy participants are more likely to remain in the study during extended follow-ups and institutionalized participants and those with (severe) health problems are more likely to drop-out (Picavet et al., 2017). Thus, participants of this study possibly represent a slightly healthier part of the population. Also, our study population is less representative of those living in more urbanized regions. Second, we had to include random blood glucose instead of fasting glucose in the HAI score. Consequently, our values for glucose were less accurate, although we took this into account in the chosen cut-off points. Third, we considered all respondents aged 45 years and younger cognitive healthy which may be an incorrect assumption. This may also explain partly why we found that '*Gradual agers*' were slightly younger. The study has the following strengths. First, the long follow-up time and high participation rate provided us the opportunity to study the HAI longitudinally. Second, the wide age range (25–65 years at T1) of the respondents provided new insights in the HAI. Third, the HAI was measured consistently by trained health care professionals which ensured reliability.

4.2. Conclusions and policy implications

This study showed that there is significant variation in physiological aging, with a substantial difference in healthy life years: the '*early*' aging men have the potential to gain approximately five healthy life years between the ages of 30 and 70 if they can transit to the '*gradual*' aging trajectory. This study also showed that a large part of the life course is relevant for 'physiological aging': aging starts fairly early in life. Considering the main characteristics associated with aging trajectories, policies targeting to improve educational attainment and to promote a healthy life style, leading to adequate BMI levels (i.e., to promote sufficient physical activity and a healthy diet), seem important to physiological aging. And these policies should target the whole population, not just older people, as aging seems to starts early in life. Furthermore, for early identification of those at risk for 'early aging', which is needed for targeting preventive interventions, the monitoring of both life style risk indicators and HAI indicators may be relevant.

CRediT authorship contribution statement

Charlotte M. Dieteren: Conceptualization, Methodology, Data curation, Writing - original draft, Formal analysis. **Leonard D. Samson:** Conceptualization, Writing - review & editing, Visualization. **Maarten Schipper:** Methodology, Formal analysis. **Job van Exel:** Conceptualization, Writing - review & editing. **Werner B.F. Brouwer:** Writing - review & editing. **W.M. Monique Verschuren:** Resources, Writing - review & editing. **H. Susan J. Picavet:** Conceptualization, Resources, Writing - review & editing.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2020.106193.

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