Determinants of reaching human longevity

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DISSERTATION

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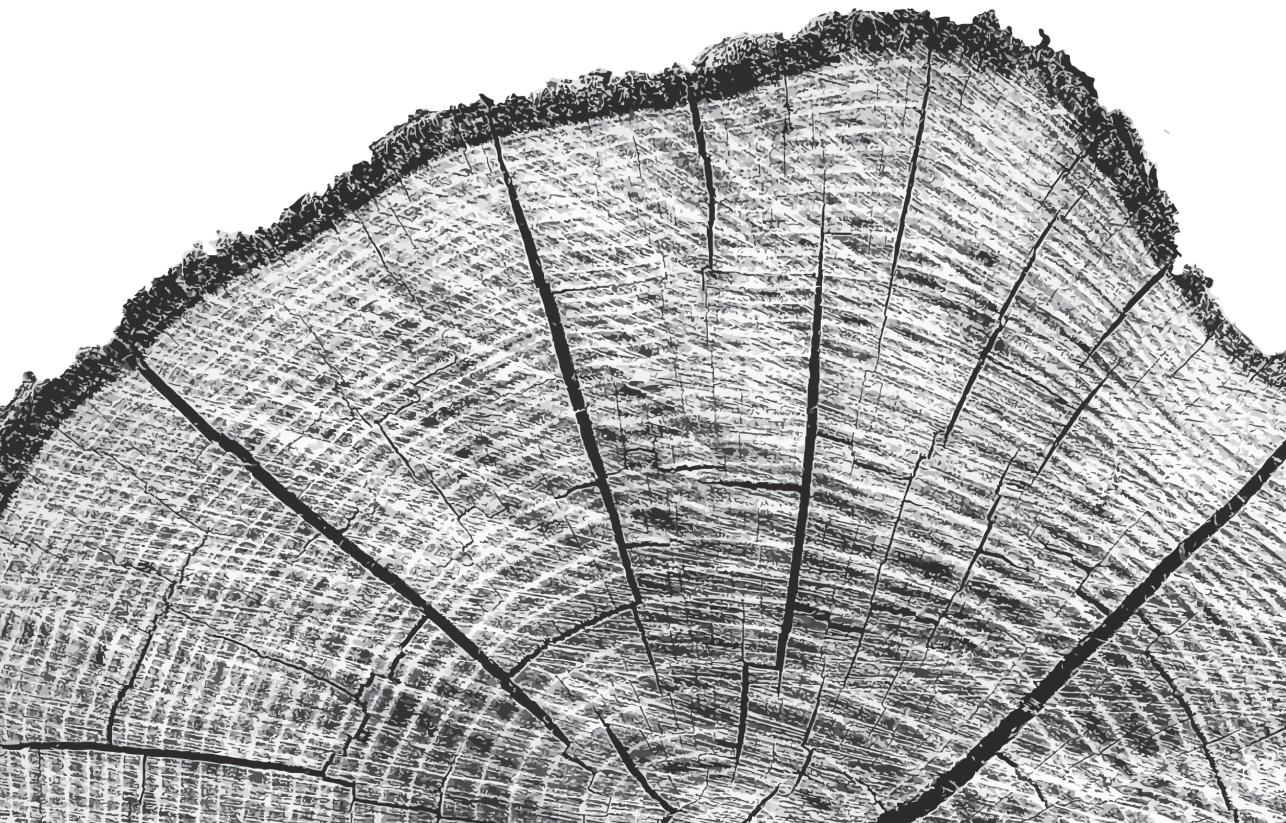
Chapter 1
General Introduction



Human longevity refers to individuals who live exceptionally long compared to other members of the populations from which they stem. They belong to a selective group of individuals who have been able to withstand the test of time successfully. Although the exact definition of longevity often differs across (study)populations and over time, longevity is mostly defined as reaching a specific age that exceeds the life expectancy (e.g. age 85 or 90 years), or by exceeding a survival percentile threshold (e.g. top 10%) of their birth cohort (1-5). There is increasing evidence that in those who reach exceptional ages, the development of chronic diseases is also delayed (6, 7). As a result, there is a growing research interest in factors that characterize this group of exceptional survivors (1, 8). Although a longer lifespan is generally positive, reaching longevity might also be accompanied by some negative side effects. For instance, because people live longer than the average life expectancy they might outlive their resources, family and friends, which could lead to poverty and feelings of loneliness. Additionally, the very old often need structural assistance with activities of daily living (ADL), which is a major healthcare cost for both society and the individual.

Human lifespan

There is much variation in the duration of lifespan (the time between birth and death) within and between species. Evolutionary, organisms have evolved by optimizing the reproductive capabilities of their species. Organisms had to find a balance between growth, reproduction and DNA repair maintenance. A well-developed repair and maintenance mechanism only evolves when a longer lifespan optimizes the reproductive capabilities of the species. This balance depends heavily on the level of environmental hazards to which the organism is exposed. Longevity could be beneficial in a stable environment with little external threats. If there are a lot of external threats that lead to early mortality, it is not beneficial to invest heavily in maintenance. Instead, it would be more beneficial to invest in rapid growth and reproduction as an optimal strategy for ensuring offspring. Evolutionary, early mammals have experienced many environmental hazards that led to early mortality of individuals. As a result, most modern mammals, including humans, have only a limited repair capacity. Consequently, damaged somatic cells will go into senescence and accumulate over time, which results in aging of the body (9). It has been hypothesized that by natural selection the human body has evolved to maximize its fitness until the end of its reproductive lifespan.

Several evolutionary theories have been proposed to explain why humans tend to age when their sexual maturity ends, a period that is often referred to as the “selection shadow” (10). In 1952, the mutation accumulation theory was proposed (11). This theory stated that mutations that affect health are selected against during the reproductive lifespan. However, mutations that affect health at a later age (during the selection shadow) are not selected against, and these late-acting mutations accumulate in the population (11). Building on this theory, Williams (1957) formulated the antagonistic pleiotropy theory (12). This theory describes a phenomenon where one gene controls for more than one genetic trait (pleiotropy), of which at least one is beneficial and at least one is detrimental (antagonistic). The theory states that genes are selected by their beneficial effect to the reproduction and fitness in an organism’s early life, despite their potential detrimental effect in later life (12). This theory is often used as

an explanation for the survival of non-optimal alleles that increase the rate of aging and/or the risk for certain genetic disorders (e.g. Huntington's disease) in later life. In line with these evolutionary theories, the disposable-soma theory was proposed in 1991 (9). This theory describes that somatic cells are maintained for reproductive success and that they become disposable after the reproductive lifespan.

In humans, the exposure to external lethal hazards in early life has been reduced in the last two centuries. As a result, the average lifespan has increased and factors influencing the rate of somatic senescence beyond the reproductive lifespan became increasingly important. The most commonly used measure to estimate the average lifespan in a human population is the period life expectancy at birth (period LEB). This measure expresses the average duration of life of a hypothetical cohort in a given year (13). Period life expectancies use the age-specific probabilities of death (mortality rates) of a single calendar year (or group of years) and project these probabilities on the life course of the hypothetical cohort. This also means that future changes in mortality rates are not taken into account.

Worldwide, the LEB has been increasing substantially since the start of the twentieth century. In 1900, the LEB was 32.0 years, which increased to 71.4 years in 2015 (14). In developed countries, the LEB showed an even stronger increase. For instance, in 1900, the LEB in Europe was 42.7 years (14). This has increased to age 62 years in 1950, and to age 78.5 years in 2019 (14, 15). In the United States the LEB increased from 49.2 years in 1900 to 78.8 years in 2015 (16, 17). The strongest increase in LEB occurred in Japan, with 38.6 years in 1900 to 83.8 years in 2015 (15). In the Netherlands, the LEB was 48.0 years in 1900 and 81.8 years in 2018 (18, 19).

In the first half of the twentieth century, the growing LEB among humans could be attributed to reduction of mortality in early life (20). Improved personal hygiene and the implementation of vaccination reduced premature deaths caused by air- and waterborne infectious diseases (21). It is estimated that the reduction of infection diseases has contributed to 55-80% of the total mortality decline observed between 1875 and 1970 in the Netherlands (20). Improved nutrition and increased food availability by improved storage and transportation, have led to further reductions in childhood mortality (21). Although the largest reduction of mortality was observed in early life, the remaining life expectancy at older ages has also increased. In the Netherlands, the life expectancy at age 65 has increased from 14.7 years in 1950 to 20.3 years in 2018 (18). After 1970, reduction in cardiovascular deaths and reduced deaths by external causes (e.g. traffic accidents contributed 74% of the total decline in mortality, because the number of deaths due to infection diseases was already low (20, 22).

Due to the reduction of infectious diseases, more people are reaching the "selection shadow". Still, there is a lot of variation in the lifespan between people after their reproductive lifespan. Exposure to accidental traumas resulting in death will explain a part of the variation, but still some people seem to age faster than others. Several theories have been proposed to explain how people age. In general, these theories can be classified in one of two overarching categories, namely programmed- or error-

theories of aging (10, 23). Programmed theories assume that aging is an active process, that depends on biological clocks that regulate gene-signaling to the nervous, endocrine and immune systems depending on the stage of life (24-27). On the other hand, error theories state that aging is a (passive) process of error accumulation (e.g. free radical theory, accumulation of (mitochondrial) DNA damage, and protein cross-linking (28-31)). Aging is most likely not explained by a single theory, but rather a multifactorial process that incorporates several elements of the above mentioned programmed and error theories.

Together with an increasing life expectancy, reaching an exceptionally old age seems to become more common in recent decades as well. People who have reached longevity seem to have a decreased rate of aging compared to the population from which they stem. For women aged 65 years in the Netherlands, the probability of reaching the age of 90 years was 9.4% in 1950, and increased to 27.9% in 2000 (Table 1). For men, this probability increased from 8.3% to 12.8% (Table 1). These figures indicate that the increased probability of reaching old ages during the second half of the twentieth century is mainly attributable to the increased probabilities in women. Worldwide, it is expected that the absolute number of persons reaching the age of 90 years will quadruple by the year 2060 (32). Historically, human longevity has fascinated humanity, and many researchers have tried to identify factors that might prolong the lifespan.

Table 1. Sex-specific percentages of survival to the age of 90 years at the age of 65 years in the Netherlands (1950-2000), Statistics Netherlands (CBS)(18).

	Likelihood of survival to age 90 years at age 65 years (%)	
Year	Men	Women
1950	8.3	9.4
1960	9.3	12.5
1970	9.1	15.8
1980	10.6	24.1
1990	10.8	26.7
2000	12.8	27.9

Methods studying determinants of reaching human longevity

Apart from anecdotal case reports about the lifestyle of centenarians, several researchers have tried to investigate determinants of reaching human longevity using a population-based study approach. Some studies have studied longevity using a retrospective or case-control design (e.g. (33-37)). However, these studies are often hampered by recall-bias of the exposure or inappropriate selection of deceased and/or younger controls. Sometimes, historical data can be used to determine the exposure status or certain demographic characteristics of an individual in the past e.g. (38-40). Although these data are often a valuable and reliable source of information, data on other relevant confounding factors are not available which might lead to confounding bias.

Due to the rise of large prospective cohort studies to study the etiology of chronic diseases since the mid-twentieth century, prospectively collected individual data of those who became very old are becoming increasingly available (41). As a result, researchers have recently gained new possibilities to investigate how baseline characteristics of those who reached an exceptional lifespan differ from those who had a shorter lifespan. In a prospective cohort study, a random cohort of individuals is sampled from a target population of a certain age range. After recruitment of the cohort, exposure information of the participants is collected by questionnaires, diaries, interviews and/or by the collection of biological samples (e.g. blood, nails, saliva). These participants are then followed over time (which might take several decades) to observe the incidence of diseases, mortality, and/or other outcomes of interest. Statistical analyses techniques can then be used to evaluate the relationship between an exposure and the outcome under study, while accounting for other potential relevant variables that might explain the association. For studies on longevity, reaching a certain longevity cut-off age (e.g. reaching 90 years (yes/no)) is used as the main outcome variable. The main advantage of this study design is that selection of participants and data collection is independent of the outcome, reducing the risk for selection and information bias. Furthermore, the amount of detailed information that is collected from the participant makes it possible to reduce the risk for potential confounding bias.

Because of the long follow-up time, and the large numbers of participants that are required to examine the etiology of rare diseases, prospective cohort studies are costly and require labor-intensive data processing and maintenance. Because of this, the number of cohort studies that have a sufficiently long follow-up to study participants who could have reached an exceptionally high age is still limited. Nevertheless, their number is growing. Most analyses defined longevity as reaching the age of 85 or 90 years, because a longer follow-up is often not possible (42-52). Reaching longevity is determined by a combination of inherited/genetic factors and environmental factors. Inheritance of longevity

Because longevity is partially determined by genes, it has been observed that longevity often clusters within families (53, 54). Several studies have investigated the heritability of longevity with varying study designs and results. Most studies used cross-sectional analyses comparing multiple cohorts, or cases to younger controls using historical genealogical data, as summarized in (2). Van den Berg et.al. (2017) stated that parental lifespan was positively associated with offspring lifespan in all twelve studies investigating this relationship, with most evidence for a mother-daughter longevity relationship (2). Other studies used a prospective cohort approach to study the relationship between parental longevity and offspring longevity , which we reviewed in 2016 at the start of the PhD trajectory. This is described in chapter 2. These studies have shown inconsistent results. Therefore, replication of these findings in other cohorts is needed. It is estimated that approximately 20-30% of human longevity can be attributed to genetic factors (55, 56). To date, single nucleotide polymorphisms (SNPs) in the Apolipoprotein E (ApoE) gene, and the forkhead box O3A (FOXO3A) gene are the most important genetic alterations associated with longevity (56, 57). The presence of the ApoE ε4 allele has been negatively associated with longevity, while

the presence of the ApoE ε2 allele has been positively associated with longevity, compared to the presence of the ApoE ε3 allele (57-59). Several SNPs in the FOXO3A gene, which is linked to the insulin/insulin growth factor-1 (IGF-1) signaling pathway, have been positively associated with longevity and healthy aging (57, 60-62). Several other genes have been suggested to be associated with longevity, including Sirtuin 1 (SIRT1), target of rapamycin (mTOR), angiotensin converting enzyme (ACE), nitric oxide synthase (NOS) gene, but these have shown inconsistent results (56).

(Modifiable) lifestyle factors and longevity

The findings regarding genetic factors and longevity indicate that human longevity is mainly determined by non-genetic, and potentially modifiable factors. It is known that exposure to certain environmental factors could lead to somatic cell damage and an increased amount of DNA damage, protein cross-linking, and accumulation of free radicals. Exposure to harmful or protective environmental factors might therefore influence the rate of aging, and could potentially influence the likelihood of reaching exceptional ages. Several lifestyle factors have been associated with reaching longevity, which we reviewed more elaborately in Chapter 2. Based on this review, we concluded that smoking status, and physical activity were the most important factors that are associated with longevity. Alcohol intake, BMI, marital status and educational level have shown limited and/or contradictory associations. Still, the absolute number of studies investigating the relationship between non-genetic factors and longevity is limited.

Reproductive factors and longevity

Several evolutionary theories have argued that increased investments in growth and reproduction in early life come at the expense of repair mechanisms in later life (9, 12). Based on these theories, there seems to be an antagonistic relationship between reproduction and longevity. The lack of prospective cohort studies on the association between reproductive factors and longevity, which we described in chapter 2, was therefore surprising. More recently, some studies have started to assess the relationship between female reproductive factors and reaching longevity, defined as reaching the age of 90 years (52, 63). In these analyses, a later age at menarche, a later age at menopause, and a longer reproductive lifespan were associated with an increased odds of reaching 90 years (52). Furthermore, parity, and a later age at first childbirth were also associated with an increased odds of reaching 90 years (63).

The potential role of psychosocial factors

Although most theories of aging focus on biological mechanisms, several psychosocial factors have been associated with an increased or decreased risk for premature mortality (64-66). However, the potential relationship between psychosocial factors and longevity has received little attention thus far. Recently, two prospective cohort studies observed that optimism, and social integration were associated with an increased odds of reaching the age of 85 years (67, 68). This indicates that an increased subjective well-being might postpone aging and increase the lifespan. Therefore, it would be interesting to examine the relationship between psychosocial factors and reaching longevity.

Longevity vs. mortality

Although the number of studies on longevity is limited, more research has been performed to investigate non-genetic factors that are associated with short- and long-term mortality. The concept longevity and mortality are closely related. Therefore, studies on mortality are a valuable source for identifying potentially interesting factors that could be associated with reaching longevity as well. While studies on longevity estimate the probability of reaching an exceptionally high age, studies on mortality estimate an average risk probability of mortality for a certain time-period. This means that studies on mortality hold a strong assumption that the estimated risk is similar over the examined time-period, independent of individual differences during the aging process. During the aging process, different contextual conditions might influence the survival curve, the effect of relevant factors on mortality might converge or crossover across different stages of life, and the role of chance is substantial (69, 70). Therefore, studies on mortality are more suitable for identifying factors that are associated with premature death, which occurs at every stage of the life course, rather than identifying factors that are associated with reaching exceptionally high ages. In terms of causality, inspired by the causal pie model of Rothman (71, 72), studies on mortality might hint towards factors that act as a component cause for reaching longevity. However, these factors do not necessarily add up to a sufficient cause for reaching longevity, because the outcome (longevity) is not yet known. As a result, a factor might be associated with premature mortality and not with longevity, and vice versa. By estimating the risk of reaching an exceptionally high age, a natural selection takes place by which we are able to select those who fit the robust description of an "exceptional survivor". As a result, we can investigate how their characteristics differ from those who died at earlier ages in the same population.

Rationale and aim

Using a prospective cohort approach, we aimed to identify particular characteristics that are associated with a decreased or increased probability of reaching longevity. For the analyses in this dissertation, we defined reaching longevity as reaching the age of 90 years. Furthermore, our review (chapter 2) has addressed several knowledge gaps, and found inconsistencies between findings, which we have tried to accommodate in this PhD thesis.

Study design

For the analyses in this thesis, data from two prospective cohorts was used, namely the Netherlands Cohort Study (NLCS) for the analyses on parental, lifestyle and reproductive factors, and the Longitudinal Aging Study Amsterdam (LASA) for the analyses on loneliness.

The Netherlands Cohort Study (NLCS)

The NLCS was set up in 1986 as a large prospective cohort study, which aimed to investigate the relationship between diet and the development of multiple cancers in the Netherlands (73). The NLCS collected data from 120,852 men and women (aged 55-69 years) using an 11-page self-administrated questionnaire. This questionnaire contained questions on demographic factors, dietary habits, smoking habits, physical

activity, alcohol consumption, anthropometry, medical information, and family history. To increase efficiency in the data processing and follow-up, a case-cohort design was used. Here, a random subcohort of 5,000 people (2,411 men and 2,589 women) was sampled from the total cohort at baseline and followed up for vital status information. Furthermore, the total cohort has been monitored for cancer incidence by record linkage to the cancer registry annually, since the onset of the study (74). As a result of the case-cohort approach, only the questionnaire data from the subcohort members and incident cancer cases have been entered into the database. In addition to cancer incidence, the full 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 2011.

NLCS Longevity cohort

Because only a part of the subcohort was at risk to reach the age of 90 years at the onset of this longevity project, we were forced to look beyond the subcohort and select those participants in the full cohort who were able to reach the age of 90 years in 2011. Because most of the questionnaires from these participants still needed to be entered (given the case-cohort design aimed at cancer incidence), the data entry was restricted to the oldest birth cohorts (1916, and 1917) of the NLCS cohort. The participants from these two birth years form the longevity cohort for the current longevity analyses in the NLCS (i.e. aged 68-70 years at baseline). Follow-up for vital status of the longevity cohort until the age of 90 was 99.9% complete. Seven participants were lost to follow-up due to migration before reaching the age of 90. As a result, the study population of the longevity cohort consisted of 7,807 participants (3,646 men and 4,161 women). Our mortality follow-up showed that among these participants 565 men (15.5%) and 1388 women (33.4%) have survived to the age of 90 years.

Longitudinal Aging Study Amsterdam (LASA)

The Longitudinal Aging Study Amsterdam (LASA) is a prospective cohort study initiated in 1992 to study the physical, emotional, cognitive, and social functioning of older adults (aged 55-84 years) in the Netherlands (75). In 1992, a sample was recruited from 11 municipal registries within three representative geographic regions in the Netherlands for the Living Arrangements and Social Networks of Older Adults programme (LSN). These regions were chosen to represent the protestant north, and the catholic south, in both urban and rural areas. Participants recruited for this study were born between 1908 and 1937, with an oversampling of older individuals and males. The initial response rate was 62% (n=3,805). From this sample, 3677 surviving participants were contacted for the first LASA cycle (1992-1993) on average 11 months after the LSN interview, with a response rate of 85%. Examinations were performed at the participants' homes, and re-examinations took place about every three years. Trained interviewers held the home interviews, and additional data was obtained using a self-administered questionnaire. During the home interviews, participants were also asked for consent to participate in a separate medical interview. During the medical interview, clinical measurements were taken, and the interviewer asked additional questions.

Loneliness has been assessed during the home interviews using a validated 11-item

De Jong-Gierveld scale (76). Mortality follow-up was done by record linkage to the municipal population registries, Gemeentelijk Basisadministratie Persoonsgegevens (GBA). The last date of mortality follow-up for this study was August 1st, 2018. Because only a part of the full cohort was "at risk"of reaching the age of 90 years at this date, the analyses were restricted to participants born before August 2nd, 1928. Of these, follow-up for mortality was 99.5% complete. After exclusion of participants with missing data information on loneliness (n=62), 1,032 men and 1,078 women were included for these analyses. Our mortality follow-up showed that among these participants 252 men (24.4%) and 413 women (38.3%) have survived to the age of 90 years.

Thesis outline

The studies of this thesis aimed to identify potential non-genetic determinants that are associated with reaching longevity. The thesis starts with a literature review (chapter 2), in which we provided an overview of prospective cohort studies that have aimed to assess the relationship between parental, lifestyle and reproductive factors and the chance/odds of reaching longevity defined as reaching a certain longevity cut-off age (75-100 years). In chapter 3 we describe inheritance patterns of longevity between parents and their offspring within the NLCS. In chapter 4, 5, and 6 we describe how several lifestyle factors in later life are associated with reaching the age of 90 years. These lifestyle factors include several smoking habits (chapter 4), body size and non-occupational physical activity (chapter 5), and alcohol consumption (chapter 6). In chapter 7 we describe how several reproductive factors in women are associated with the probability of reaching 90 years of age. In Chapter 8 we describe whether loneliness is related with the probability of reaching 90 years of age, using data from the LASA study. Lastly, in Chapter 9, the findings of this thesis are discussed, and put into perspective.

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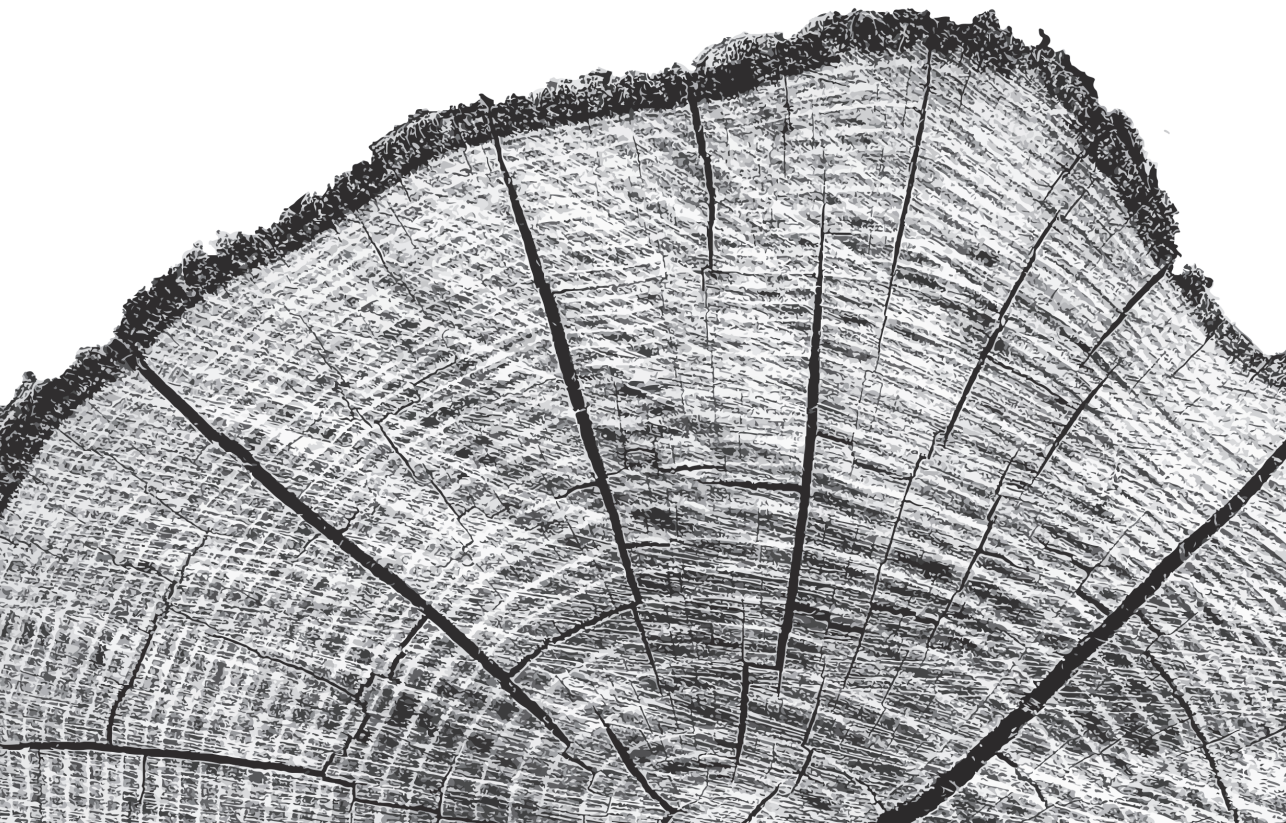
Chapter 2

Lifestyle, parental and reproductive determinants of longevity: a review of epidemiological data.

Lloyd Brandts, Dalia Shash, and Piet A. van den Brandt



Lifestyle, parental and reproductive determinants of longevity: a review of epidemiological data.

Lloyd Brandts, Dalia Shash, Piet A. van den Brandt

Abstract

Background
With an increasingly aging population, societies need to adapt to the challenges and issues associated with it. Therefore, extending our knowledge on (modifiable) factors that may contribute to an increase or decline in human longevity is very important in order to predict future trends in aging. This paper aimed to summarize the available data on lifestyle, parental and reproductive factors and their association with longevity.
Methods
A literature search was conducted using PubMed to identify publications assessing the association of these factors with longevity. Study results were summarized and assessed for differences due to the longevity cut-off age, age at baseline measurement, and subgroup if possible. Furthermore, we identified gaps in the available data.
Results
Thirteen publications on cohort studies were included for this review. Differences were found across studies regarding longevity cut-off age and age at baseline. Among the factors of interest, smoking and physical activity seem to be important factors associated with longevity. Alcohol consumption, coffee consumption, Body Mass Index, education, marital status, and parental longevity show limited and/or contradictory results and need further assessment. In addition, there are almost no data regarding the association of dietary and reproductive factors with longevity.
Conclusions
This review highlights the current knowledge and gaps in longevity research. Given the limited number of publications on this topic, more research on longevity among men and women should be done to gain insight into the epidemiology of longevity.

Introduction

One of the biggest developments that will confront us in the future is the changing demographic composition of the human population. The absolute number of elderly reaching 90 years of age is expected to quadruple by 2060 (1). However, some speculate that the rise in life expectancy might flatten or even decline in the future, due to an increasing proportion of obese, and physically inactive individuals (2, 3). Because demographic changes have huge implications for societal policies, it is important to understand the underlying determinants of longevity.

There are various theories on how longevity is attained but most researchers agree that aging is a multifactorial process that is subject to hereditary and environmental influences (4-6). It is estimated that genetic influences account for 25% in the process of reaching longevity (7, 8). This indicates that the remaining influences are largely environmental and therefore potentially modifiable. Multiple studies have tried to assess determinants of longevity using various approaches. Rizzuto and Fratiglioni (9) have reviewed the relationship between potentially modifiable factors and mortality risk in elderly. Based on multiple studies and systematic reviews, they found that smoking, body mass index (BMI), social networks, physical activity, and leisure time activity were the most important predictors for mortality in elderly (9). Another review suggested reproductive phenotypes, including age at menarche and age at menopause, to be important factors explaining the longevity advantage in women (10). Most of these findings were based on short- and long term mortality analyses in elderly populations. However, a variable could show an association with short term mortality, while not with longevity, leading to inconclusive interpretations of the results and their relevance to longevity. When assessing longevity the outcome should be defined as reaching a specific old age. Factors with stronger associations to longevity could otherwise be missed if the focus is on mortality over a certain follow-up period. In addition, many researchers conducted cross-sectional analyses comparing groups from different birth cohorts or different populations instead (11-14). As a result, the observed effects could be due to generational or group differences that are almost impossible to account for.

We aimed to summarize the available publications on determinants of longevity, defined as reaching a certain age compared with not reaching that age. The criteria for defining longevity have evolved throughout the years because of an increasing life expectancy worldwide (15). The cut-off age for defining longevity varies between studies, but is often between 75 and 100 years of age. (16-19). Furthermore, some studies use age categories (e.g. octogenarians (80-89 years), nonagenarians (90-99 years), and centenarians (100+ years)) to specify longevity (20). For this review, studies with longevity cut-off points from 75 years of age and over were used. Moreover, the focus is on studies assessing lifestyle, parental and reproductive factors, instead of genetic markers and their association to longevity, as these have been recently reviewed (8). Although parental longevity and reproductive factors are not necessarily modifiable, they may help to understand the aging process and can be easily assessed in an observational setting. Furthermore, growing evidence suggests an association between parental influences and the health of

subsequent generations (21-23). With this paper we provide a literature review with available data on the relationship between lifestyle, parental and reproductive factors, and longevity.

Methods

A literature search was conducted using PubMed. The final search algorithm was created out of five building blocks to identify publications using MESH terms and keywords in titles and abstracts. We aimed to identify publications relating modifiable lifestyle, parental or reproductive factors with longevity. The search was further restricted to publications between 01 January 1990 and 31 October 2016 in human species. The final search term was as follows: *"(((“Aged, 80 and over”[MeSH Terms]OR “Aged”[MeSH Terms]) AND (“Cohort Studies”[MeSH Terms] OR (Reach*[tiab] AND age[tiab])) AND (“Longevity”[MAJR] OR “Life Expectancy”[MAJR] OR (“Aging/physiology”[MAJR]) OR “Aging/genetics”[MeSH Terms])) AND (“Life Style”[MeSH Terms] OR “Risk Factors”[MeSH Terms] OR “Behavior”[MeSH Terms] OR “Diet”[MeSH Terms] OR “Body Constitution”[MeSH Terms] OR “Family characteristics”[MeSH Terms] OR “Socioeconomic factors”[MeSH Terms])) OR ((longevity[tiab] OR Life Expectanc*[tiab] OR octogen*[tiab] OR nonagen*[tiab] OR centen*[tiab]) AND Surviv*[tiab]) AND (lifestyle[tiab] OR (modifi*[tiab] AND factor*[tiab]) OR (reproductive[tiab] AND factor*[tiab]) OR (parental[tiab] AND factor*[tiab]) OR (exceptional[tiab] AND surviv*[tiab]))”.*

In addition to searching the database for publications, we checked the references of the publications included in this review and in reviews published earlier. We included studies that defined longevity as reaching a certain cut-off age, with a prospective cohort design, and that assessed the effects of lifestyle, parental, or reproductive factors on longevity. We excluded: studies that assessed mortality over a certain follow-up period, studies that investigated longevity cut-off ages below 75 years, studies with a cross-sectional design, or studies that investigated longevity within cohorts of patient groups.

After identification of the publications, the studied lifestyle, parental and reproductive factors were identified and the respective results summarized. The included studies were heterogeneous in terms of the outcome (cut-off age), baseline age, population used, and length of follow-up. In addition, some variation was present in categorizing levels of exposure. Therefore, no statistical pooling methods were used for this review. We presented study specific results, yet we aimed to identify patterns across studies that are related to the longevity cut-off age, differences in the start of the baseline period, or the definition of the factors of interest. The effect estimates including 95% confidence intervals (95% CI) were used to describe the direction of associations between the factor of interest and the chance of reaching longevity. As some studies assessed survival to a longevity cut-off age and others mortality to a longevity cut-off age, the inverse of the effect ratio was calculated if needed, to make effect estimates comparable. Many publications did not present effect estimates if no association was found, therefore these estimates could not be presented (16-18, 24, 25).

Results

From the 511 records found in PubMed, twelve articles were found eligible based on our in- and exclusion criteria (16-20, 24-30) (Figure 1). In addition, one article was identified when references were checked (31). The longevity cut-off points that were used in these studies ranged from 75 years of age to 100 years of age. Age at baseline ranged from age 40 to 72 years (Figure 2). The average follow-up period was 31.6 years (range, 15-45 years). Furthermore, seven studies included both men and women (16-18, 25, 29-31), and six only included men (19, 20, 24, 26-28).

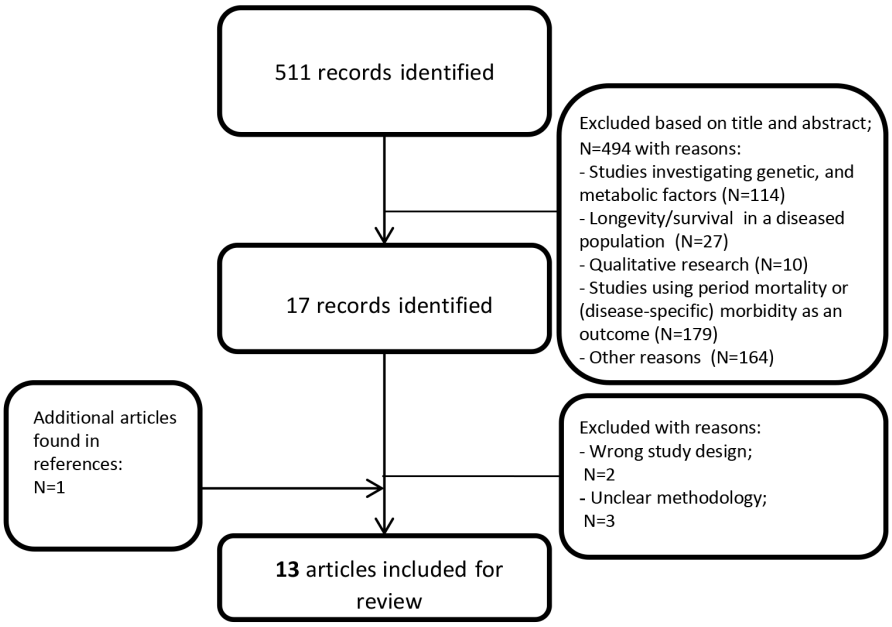


Figure 1: Flowchart of search strategy results, additional results and number of excluded publications.

Description of cohort studies

Among the thirteen included articles, nine separate cohorts were identified of which five originated from Europe (17, 18, 25, 27, 28, 30) and four from the United States (US) (16, 19, 20, 24, 26, 29, 31). Two articles used data from the Framingham Heart Study (FHS) (16, 31). Set up in 1948, the FHS aimed to identify risk factors for cardiovascular disease. The FHS longevity publications assessed factors measured in around 2,500 healthy middle-aged adults of 50 years who were followed up until they reached 75 years of age (16), or 85 years of age (31). Another publication used data from the Physicians' Health Study (PHS), and was started in Massachusetts, USA in 1982 to test the benefits and risks of aspirin and beta-carotene (19). The authors assessed the association between factors measured in 2,357 healthy men of at least 66 years of age (mean age 72) and longevity (90 years) (19).

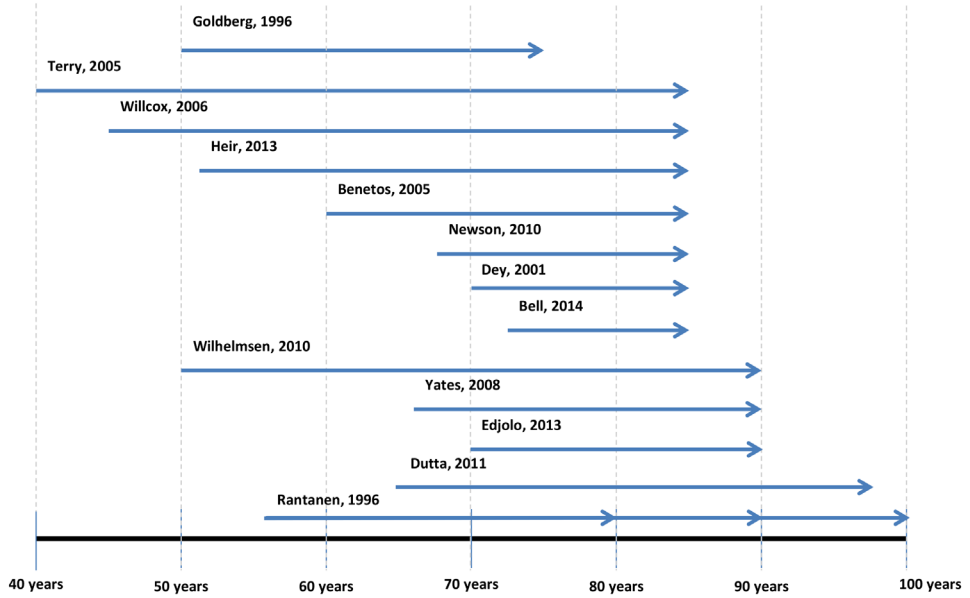


Figure 2: Study follow-up time from age at baseline to longevity cut-off point. Studies sorted by longevity cut-off age, and then by baseline age.

There were three US publications based on data from the Honolulu Heart Program (HHP) (20, 24, 26). Originally, the HHP aimed to investigate the aetiology of coronary heart disease and stroke among healthy American men of Japanese ancestry who were living on the island of Oahu in 1965. They measured the participants' baseline characteristics twice, once at mid-life (45-68 years) and once in late life (72-82 years). The three selected HHP publications had a different focus: The first one quantified the association between factors measured in mid-life(mean age 54) and survival to 85 years of age in 5,820 healthy men (26). The second used factors measured in 2,239 healthy older adults (mean age 76) and also studied their association with survival to the age of 85 years (24). The third study included those with the potential to reach 100 years within the considered follow-up period, leaving 1,292 healthy men aged 56-68 years (mean age 62), and analysed the association between factors measured at that age and the chance of reaching octogen-, nonagen- or centenarian status (20). The last publication originating from the US used data from the Iowa-Established Populations for Epidemiologic Study of the Elderly (Iowa-ESEPE) (29). This prospective cohort study was initially set up to identify risk factors for mortality, institutional admissions, and changes in functional abilities. They analysed 2,890 community-dwelling citizens, who were between 65 and 85 years of age at baseline (November 1981-January 1983), and followed them up to death. Separate analyses were performed within men, and women using the top 10th percentile survivors cut-off age as an outcome (94 years for men, 97 years for women).

There were six European studies (17, 18, 25, 27, 28, 30), five of which were based on existing cohort studies (18, 25, 27, 28, 30), and one based on data from a standard examination program (17). The first used data from the Oslo Ischemia Study (OIS) (28). The OIS aimed to detect unsuspected coronary heart disease. For the publication of Heir et al. (2013), 821 men were followed up from 51-59 years to 85 years of age. The analyses were conducted separately for smokers and non-smokers (28). The second study was based on the Rotterdam study (18). The main objectives of the Rotterdam Study were to investigate the risk factors of cardiovascular, neurological, ophthalmological, and endocrine diseases in the elderly. For this study, they followed up 2,008 men and women from 68 -84 years and assessed their survival to at least 85 years of age (18). The third study was based on the existing PAQUID cohort, which is a French study initiated to better understand dementia in the elderly (25). 2,578 participants were followed up to assess the association between risk factors measured at age 70 years or older and survival to 90 years of age. Another French study used national standard examination data from IPC centers (Centre d'Investigations Préventives et Cliniques) and followed 7,467 participants from 60-70 years of age to 80 years (men) and 85 years (women) (17). They assessed the association between factors measured at baseline and reaching longevity. The authors analysed males and females separately and together (17). Finally, two studies used data from the Swedish Gothenburg cohort (27, 30). One study assessed determinants of longevity to the age of 90 in 855 men measured at 50, 54, 60 and 67 years of age (27). The other study analysed both men (n=1,225) and women (n=1,403) from 70 years until 85 years of age (30). A summary of the studies described above can be found in Table 1.

Table 1: Overview of identified publications sorted by publication year.

Reference	Design	Follow-up	Age at baseline	Outcome	Analysis
Goldberg, 1996 (16)	Cohort: Framingham Heart Study(FHS), Framingham, USA Sample size: 1,720 men, and women free of certain diseases[a]	1948-52 to early 1990s	50 years	Survival to the age of ≥75 years	• Males and Females were analysed separately • Adjustment factors considered were Italian ancestry, education, marital status, occupation, alcohol intake, smoking, hypertension, level of systolic and diastolic blood pressure (SBP, DBP), Body Mass Index (BMI), current heart rate, forced vital capacity (FVC), Parent's survival to 75

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Dey, 2001 (30)	Cohort: Gothenburg, Sweden. Sample size: 2,628 men and women	1971-81 to 1996	70 years	Survival to the age of 85 years	• Males and Females were analysed separately • Adjustment factors considered were birth cohort, smoking habits at age 70, and weight change between 70 and 75 years.
Benetos, 2005 (17)	Cohort: Participants of standard IPC Center examinations in Paris area, France Sample size: 7,467 men and women	1972-81 to 1997	60-70 years	Men: Survival to the age of ≥ 80 years Women: Survival to the age of ≥85 years	• Males and Females were analysed together and separately • Adjustment factors considered were age, gender, personal history of diseases, Forced expiratory volume (FEV) ratio, SBP, DBP, pulse pressure (PP), total cholesterol, glycaemia, smoking, BMI, triglycerides, heart rate, physical activity and left ventricular hypertrophy (LVH)
Terry , 2005 (31)	Cohort: GFramingham Heart Study(FHS), Framingham, USA Sample size: 2,531 men and women free of certain diseases[a]; all born before Jan 1st 1919	1948-52 to 2004	40-50 years	Survival to the age of ≥85 years	• Adjustment factors considered were sex, SBP, DBP, PP, antihypertensive medication use, total serum cholesterol, BMI, glucose intolerance, LVH, smoking, education and physical activity index, calendar decade
Willcox, 2006 (26)	Cohort: Honolulu Heart Program (HHP), Oahu, Hawaii, USA Sample size: 5,820 Japanese American men free of certain diseases[a]; all born between 1900 -19	1965-68 to 2005	45-68 years (mean age 54)	Survival to the age of ≥85 years	• Adjustment factors considered were BMI, grip strength, hypertension, hyperglycaemia, triglycerides level, haematocrit level, uric acid levels, smoking, alcohol, education, marital status, FEV

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Yates, 2008 (19)	Cohort: Physician's Health Study (PHS), MA, USA Sample size: 2,357 men free of certain diseases[a]; all born on or before Dec 31, 1915	1981-84 to 2006	≥66 years (mean age 72)	Survival to the age of ≥90 years	• Adjustment factors considered were age, BMI, smoking status, alcohol intake, exercise frequency, history of hypertension, diabetes, high cholesterol level, angina, and treatment assignment at baseline
Newson, 2010 (18)	Cohort: Rotterdam Study, Rotterdam, The Netherlands Sample size: 2,008 men and women free of certain diseases[a] all born on or before Jan 1, 1922	1990-93 to 2007	68 - <85 years (mean age 75.8)	Survival to the age of ≥ 85 years	• Adjustment factors considered were age, sex, number of relatives, living status, income, health insurance, self-rated health, smoking, education, spousal death, BMI, energy intake, fruit and vegetable intake, alcohol intake, diabetes, atrial fibrillation, family history of morbidities, depression history, hospitalization, cognitive status, hip fracture, vertebral fracture, glucose, high density lipoprotein (HDL), cholesterol, lumbar spine bone mineral density (BMD), (instrumental) activities of daily living (I)ADL, C-reactive protein (CRP), creatinine, uric acid, albumin, femoral neck BMD, DBP, heart rate, ankle brachial index, aortic calcification, intima media thickness, carotid plaques, leucocytes, LVH • Effect modification by gender assessed

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Wilhelmsen, 2010 (27)	Cohort: Gothenburg, Sweden Sample size: 855 men born in Gothenburg in 1913 on dates divisible by 3 and who responded to the invitation to participate	1963 to 2003	50 years; factors also measured at 54, 60 and 67	Survival to the age of ≥ 90 years	• Adjustment factors considered were smoking, coffee consumption, alcohol-related problems, socio-economic status (SES), dyspnoea on exertion, psychological stress, presence of diabetes mellitus, early death or myocardial infarction (MI) in parents, blood pressure, BMI, waist circumference, blood levels of lipids and glucose, plasma fibrinogen, lung function, maximum working capacity and heart volume. The following factors were also considered but not measured at each time point: physical activity, mental stress, diabetes, height, weight and marital status
Dutta, 2011 29)	Cohort: Iowa, Established Populations for Epidemiologic Study of the Elderly (Iowa-EPESE), IA, USA. Sample size: 2,890 community-dwelling citizens.	1981-1983 to cohort 'death'	65-85 years at baseline. (mean age 72 for men, 74 for women)	Survival to the top 10% longest survivors for their gender. (94 years males, 97 years females)	• Analyses were performed separate for men and women and combined. • Adjustment factors considered were age at baseline, sex, smoking-, attitude towards life-, self-reported health-, chronic medical condition-, systolic blood pressure-, numbers of words recalled-, and gross mobility & physical ability at baseline.

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Rantanen, 2012 (20)	Cohort: Honolulu Heart Program (HHP), Oahu, Hawaii, USA Sample size: 2,239 Japanese American men free of certain diseases[a]; all born between 1900 -09 Subgroups: Males only	1965-68 to 2009	56-68 years (mean age 62)	Survival categorized as; 56-68 to < 79 = reference, 80-89 years = octogenarian, 90-99 years = nonagenarian, 100 years= centenarians	• Models repeated to assess odds of becoming centenarian, nonagenarian or octogenarian compared to dying by 79 years in tertiles of baseline grip strength • Adjustment factors considered were diabetes, high blood pressure, physical activity, mother's age and smoking
Edjolo, 2013 (25)	Cohort: PAQUID prospective cohort on brain and functional ageing, South-West France Sample size: 2,578 men and women	1988 to 2008	≥70- <90 years	Survival to the age of ≥ 90 years	• Analysis conducted separately for men and women • Adjustment factors considered were lifestyle factors, such as physical activity, smoking, alcohol intake, BMI, diet; material environment factors such as occupation, education; social environment factors such as marital status, living arrangement; current health status including cognition, depressive symptoms and impairment, self-reported history of health, perceived health and satisfaction of life, family background of siblings and parental age at death and age at birth
Heir, 2013 (28)	Cohort: Oslo ischemia study, Oslo, Norway Sample size: 821 men born no later than Dec 31, 1921, free of certain diseases[a] and without regular drug intake	1972-75 to 2006	51-59 years	Survival to the age of ≥ 85 years	• Analysis was performed separately for smokers and non-smokers • Adjustment factors considered were age, BMI, physical fitness, cholesterol level, systolic blood pressure, and daily number of cigarettes

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Bell, 2014 (24)	Cohort: Honolulu Heart Program (HHP), Oahu, Hawaii, USA Sample size: 1,292 Japanese American men participants free of certain diseases[a]; all born between 1900 -19; excluded those who did not participate in second examination in 1991-93	1991-93 to 2012	72-82 years (mean age 76)	Survival to the age of ≥ 85 years	• Adjustment factors considered were age, education , unmarried in late life, BMI, waist hip ratio, FEV, SBP, DBP, hypertension, cognitive abilities, ankle-brachial index, depression, self-rated health, triglycerides, HDL, glucose, fibrinogen, white blood cell count, insulin, total cholesterol, smoking, alcohol use, physical activity, blocks waked per day

a Diseases can vary from study to study, but usually include chronic diseases, such as cardiovascular diseases, respiratory diseases, cancer, liver and or kidney disease.

Lifestyle factors and longevity

Smoking

Twelve of the thirteen included studies estimated the association between smoking and longevity (16-20, 24-29, 31). Nine studies performed analyses within male participants (16, 19, 20, 24-29), three studies analysed female participants (16, 25, 29), and four studies combined gender in their analyses (17, 18, 29, 31). Ten studies categorized smoking in either current-/ ever- /never smoker or ever-/ never smoker (17-20, 24-27, 29, 31). In males, being an ever- or current smoker at baseline seems to be significant negatively associated with surviving to exceptional ages compared with never smokers (Table 2) (19, 20, 24-27). When both genders were combined in the analyses, three studies did find similar significant negative associations between smoking status and longevity (18, 29, 31), while one did not (17). Two publications investigated longevity in women, and both did not find a significant association between smoking status and longevity (Table 2) (25, 29). Two studies assessed the association between the numbers of cigarettes smoked per day and the odds for reaching the age of 75 years (16), and 85 years (28) respectively. Within the FHS cohort they found an odds ratio (OR) of 0.72 (95% CI, 0.62- 0.85) and 0.63 (95% CI, 0.55- 0.74) for males and females respectively per increase of 1-SD cigarettes consumed per day and reaching 75 years of age (16). Another study, which investigated men included in the OIS cohort, found ORs of 0.68 (95% CI, 0.45-1.02) and 0.39 (95% CI, 0.26-0.58) for 1-9, and ≥10 cigarettes per day, respectively, compared to non-smokers (28). This indicates an inverse dose-response relationship between the number of cigarettes smoked per day and the odds for reaching longevity. One study within the HHP cohort investigated the association between smoking status and longevity using different longevity cut-off ages (20). For ever smokers they observed an increasing strength in ORs, 0.74 (95% CI, 0.59-0.92), 0.47 (95% CI, 0.37- 0.60), and 0.17 (95% CI, 0.09-0.33)

for ever smokers, for reaching octogenarian, nonagenarian, and centenarian status respectively, compared to never smokers. This indicates that smokers are less likely to survive to older ages. Additionally, in the Gothenburg study, never smoking was significantly associated with reaching longevity (90 years) when assessed at age 50 years. However, no significant association was found between being an ex-smoker at ages 50-67 years and reaching longevity, compared to current smokers (27).

Alcohol consumption

Four studies selected for this review investigated the association between alcohol consumption and longevity in men (16, 19, 24, 26), and one in women (16) (Table 2). In the FHS cohort, they compared alcohol consumers with non-alcohol consumers and different alcohol quantities in millilitres of alcohol per week on longevity (16). They did not find a significant association between alcohol consumption and the odds for reaching 75 years of age for both sexes. In the HHP cohort, they investigated the association between drinking ≥3 alcoholic beverages a day and survival to 85 years of age (26). They found that participants drinking ≥3 beverages a day had an OR of 0.63 (95% CI, 0.53- 0.75) (inversed from original article), for surviving to 85 years of age compared with participants who consumed less alcohol. Another study in the HHP compared participants consuming >15 ounces of alcohol per month with participants consuming less, and found an OR of 0.66 (95% CI, 0.48- 0.91) for surviving to 85 years of age (24). Finally, in the PHS cohort they investigated the association between different levels of alcohol intake and survival to 90 years (19). Alcohol consumption was defined as 'drinking rarely or never' versus 'drinking 1-3 drinks per month', '1-6 drinks per week', or '≥1 drink(s) per day'. No significant associations were found when the groups were compared.

Coffee consumption

One publication from the Gothenburg cohort was found that investigated the association between coffee consumption and longevity. They found a significant OR of 0.88 (95% CI, 0.80-0.96) per increase of one cup of coffee per day for reaching 90 years of age (Table 2) (27). No studies on other dietary factors were found.

Physical activity

Six of the selected publications investigated the association between physical activity and longevity (17, 19, 20, 24, 25, 28). All studies did show a significant positive association between elevated levels of physical activity and reaching longevity compared to participants with low levels of physical activity for both sexes (Table 3) (17, 19, 20, 24, 25, 28). In addition, one study in the PHS cohort investigated a dose-response relationship between different levels of physical activity (1-4 times a month, 2-4 times per week, and ≥ 5 times a week vs. rarely or never) and the chance for reaching longevity (90 years) (19). No dose-response relationship was found across different levels of physical activity, with corresponding hazard ratios (HR) of 1.28 (95% CI, 1.10-1.49), 1.39 (95% CI, 1.20-1.61), and 1.23 (95% CI, 1.04-1.45) respectively (19). However, they found a significant positive association with longevity even at a minimal level of physical activity (1-4 times a month)

compared to those with a lower level of physical activity. In the HHP cohort, they investigated whether an increase of one hour of physical activity per day was associated with the odds of reaching different age categories (octogenarian, nonagenarian, and centenarian) (20). The effect of physical activity on reaching longevity seemed to increase with advanced ages ranging from 1.03 (95% CI, 0.99-1.06) to 1.13 (95% CI, 1.02-1.25) (20). Finally, one study that used data from the OIS cohort stratified their analyses based on smoking status (28). They found a significant association with physical activity only in non-smoking men (28).

Body Mass Index and weight change

Six studies examined the relationship between BMI (in kg/m2) and the chance for reaching a defined longevity cut-off (19, 24, 26, 28-30). Overall, these studies show varying results as presented in Table 3. All studies used different BMI cut-off points to investigate the association between BMI and longevity, which makes it difficult to formulate clear-cut conclusions. However, in general the effect estimate on longevity seems only to be significantly negatively associated in both extremes of the BMI spectrum (BMI <20, and >30) (19, 24, 28-30). Another observation is that (unintentional) weight loss, in addition to low BMI (<20), is negatively associated to longevity (18, 24, 30). Within the OIS cohort Heir et al. (28) stratified for smoking status in their analysis. They found that men with overweight (25.5-29.9 kg/m2) or obesity (>30 kg/m2) had a statistically significant lower chance for reaching the age of 85 compared to lower weight (BMI <25 kg/m2) men, but only in the non-smoking population (28). No clear differences were found between men and women.

Table 2: Associations of smoking, alcohol and diet with longevity across studies.

Reference	Cohort	Age at baseline	Longevity cut-off point	Sub-group	n	Exposure contrast definition	Effect estimate + 95% CI
Smoking							
Goldberg, 1996	FHS	50	75	Men	733	Increase of 1-sd in cigarettes smoked per day[a]	OR: 0.72 (0.62 – 0.85)[a]
				Women	946		OR: 0.63 (0.55 – 0.74)[a]
Heir, 2013	OIS	51	85	Men	821	1-9 vs. 0 cigarettes per day	OR: 0.68 (0.45-1.02)
						≥10 vs. 0 cigarettes per day	OR: 0.39 (0.26-0.58)
Terry, 2005	FHS	40	88	-	1,445	Yes (if in last year) vs. No	OR: 0.47 (0.39-0.57)
Willcox, 2006	HHP	45	85	Men	5,525	Ever vs. never	OR: 0.52 (0.46 – 0.58)[a]
Rantanen, 2012	HHP	56	80-89	Men	1,647	Ever vs. never [a]	OR: 0.74 (0.59 – 0.92)[a]
		56	90-99	Men	1,346	Ever vs. never[a]	OR: 0.47 (0.37 -0.60)[a]
		56	100	Men	848	Ever vs. never[a]	OR: 0.17 (0.09 – 0.33)[a]
Benetos, 2005	IPC	60	80 (♂)/ 85 (♀)	-	7,467	Current smoking of more than 10 cigarettes a day vs. not smoking	"No significant association"
Newson, 2010	Rotterdam	55	85	-	2,008	Ever vs. never[a]	OR: 0.74 (0.57 - 0.94)[a]

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Bell, 2014	HHP	72	85	Men	1,292	Current vs. never	OR: 0.43 (0.24 – 0.77)[a]
						Past vs. never	OR: 0.68 (0.49 – 0.68)[a]
Wilhelmsen, 2010	Gothenburg	50	90	Men	855	Never-smoker at age 50[b]	OR: 2.79 (1.75-4.44)
						Ex-smoker at age 50[b]	"No significant association"
						Stopped smoking at age 54[b]	"No significant association"
						Stopped smoking at age 60[b]	"No significant association"
						Stopped smoking at age 67[b]	"No significant association"
Dutta, 2011	Iowa- ESEPE	65	94	Men	1,080	Current vs. never[a]	OR: 0.11 (0.03-0.46)[a]
						Current vs. ex-smoker[a]	OR: 0.22 (0.05-0.93)[a]
		65	97	Women	1,683	Current vs. never[a]	OR: 0.39 (0.09-1.67)[a]
						Current vs. ex-smoker[a]	OR: 1.25 (0.19-7.69)[a]
Yates, 2008	PHS	66	90	Men	2,280	Past vs. never	HR: 0.77 (0.68- 0.86)[a]
						Current vs. never	HR: 0.48 (0.40 – 0.57)[a]
Edjolo, 2013	PAQUID	70	90	Men	1,025	Ever vs. never	HR: 0.85 (0.74- 0.99)[a]
				Women	1,492		"No significant association"
Alcohol intake							
Goldberg, 1996	FHS	50	75	Men	700	1-sd increase in alcohol intake (ml/wk)[a]	"No significant association"
				Women	916		"No significant association"
Willcox, 2006	HHP	45	85	Men	5,525	≥ 3 drinks/day vs. less	OR: 0.63 (0.53-0.75)[a]
Bell, 2014	HHP	72	85	Men	1,292	>15 vs. ≤ 15 ounces per month	OR: 0.66 (0.48-0.91)[a]
Yates, 2008	PHS	66	90	Men	2,280	1-3drinks/month vs. rarely/never	HR: 1.12 (0.90 -1.41)[a]
						1-6drinks/week vs. rarely/never	HR: 1.05 (0.90-1.23)[a]
						≥1 drink/day vs. rarely/never	HR: 1.01 (0.86-1.19)[a]
Coffee consumption							
Wilhelmsen, 2010	Gothenburg	50	90	Men	855	Increase of 1 cup of coffee per day	OR: 0.88 (0.80-0.96)

a Value or contrast definition inverted from published results. b Reference group is unclear in original publication.

Table 3: Associations of physical activity and body mass with longevity across studies.

Reference	Cohort	Age at baseline	Longevity cut-off point	Subgroup	n	Exposure contrast definition	Effect estimate + 95% CI
Physical activity							
Heir, 2013	Oslo	51	85	Non- smoking men	452	Medium vs. low	OR: 1.18 (0.71-1.98)
						High vs. low	OR: 1.88 (1.12-3.13)
				Smoking men	369	Medium vs. low	OR: 1.31 (0.72-2.39)
						High vs. low	OR: 1.80 (0.95-3.39)
Rantanen, 2012	HHP	56	80-89	Men	1,647	Increasing h/day	OR: 1.03 (0.99-1.06)
		56	90-99	Men	1,346	Increasing h/day	OR: 1.04 (1.00-1.09)
		56	100	Men	848	Increasing h/day	OR: 1.13 (1.02-1.25)
Benetos, 2005	IPC	60	80 (♂)/ 85 (♀)	-	7,467	Yes (>2h per week) vs. No	OR: 1.52 (1.27-1.83)
Bell, 2014	HHP	72	85	Men	1,292	High vs. low [a]	OR: 1.41 (1.04-1.91)
Yates, 2008	PHS	66	90	Men	2,280	1-4 times/mo vs. rarely/never	HR: 1.28 (1.10-1.49)[a]
						2-4 times/wk vs. rarely/never	HR: 1.39 (1.20-1.61)[a]
						≥5 times/wk vs. rarely/never	HR: 1.23 (1.04-1.45)[a]
Edjolo, 2013	PAQUID	70	90	Men	1,025	Regular vs. Not regular	HR: 1.35 (1.15–1.56)[a]
				Women	1,492		HR: 1.12 (1.04–1.47)[a]
BMI (kg/m^2)							
Heir, 2013	Oslo	51	85	Non-smoking men	452	25–29.9 vs. <25	OR: 0.54 (0.36-0.82)
						≥30 vs. <25	OR: 0.21 (0.05-0.96)
				Smoking men	369	25–29.9 vs. <25	OR: 0.92 (0.53–1.59)
						≥30 vs. <25	OR: 0.84 (0.17–4.12)
Willcox, 2006	HHP	45	85	Men	5,525	≥ 25 vs. <25	OR: 0.88 (0.78-1.00)[a]
Bell, 2014	HHP	72	85	Men	1,292	≥ 19 vs. <19[a]	OR: 2.25 (1.12-4.51)
						≥ 25 vs. <25[a]	"No significant association"
Yates, 2008	PHS	66	90	Men	2,280	25-29.9 vs. <25	HR: 1.03 (0.93-1.16)[a]
						>30 vs. <25	HR: 0.69 (0.53-0.91)[a]

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Dutta, 2011	Iowa-ESEPE	50	94	Men	1,092	<20 vs. 20-25	OR: 0.68 (0.14-3.29)
						25-29.9 vs. 20-25	OR: 0.73 (0.43-1.24)
						>30 vs. 20-25	OR: 0.64 (0.27-1.52)
		50	97	Women	1,698	<20 vs. 20-25	OR: 1.12 (0.52-2.43)
						25-29.9 vs. 20-25	OR: 0.87 (0.56-1.34)
						>30 vs. 20-25	OR: 0.44 (0.18-1.07)
				Combined	2,790	<20 vs. 20-25	OR: 1.00 (0.51-1.98)
						25-29.9 vs. 20-25	OR: 0.81 (0.58-1.13)
						>30 vs. 20-25	OR: 0.52 (0.28-0.96)
Dey, 2001	Gothenburg	70	85	Men	1,225	14.0-22.6 vs. 24.7-26.4	RR: 0.83 (0.66-1.04)[a]
						22.7-24.6 vs. 24.7-26.4	RR: 0.93 (0.75-1.18)[a]
						26.5-28.5 vs. 24.7-26.4	RR: 0.99 (0.79-1.23)[a]
						28.6-39.2 vs. 24.7-26.4	RR: 0.84 (0.67-1.05)[a]
				Women	1,403	14.1-22.5 vs. 24.6-26.5	RR: 0.67 (0.51-0.88)[a]
						22.6-24.5 vs. 24.6-26.5	RR: 0.86 (0.65-1.14)[a]
						26.6-29.2 vs. 24.6-26.5	RR: 0.86 (0.66-1.14)[a]
						29.3-39.8 vs. 24.6-26.5	RR: 0.8 (0.61-1.05)[a]
Weight loss							
Newson, 2010	Rotterdam	55	85	-	2,008	Unintentional weight loss (3kg in 3 months) absent vs. present	OR: 1.42 (1.04-1.94)
Dey, 2001	Gothenburg	70	85	Men	1,225	≥10% lost vs. 0-4.9% lost[b]	RR: 0.62 (0.46-0.83)[a]
						5-9.9% lost vs. 0-4.9% lost[b]	RR: 0.90 (0.63-1.30)[a]
						0-4.9% gained vs. 0-4.9% lost[b]	RR: 0.97 (0.65-1.45)[a]
						≥5% gained vs. 0-4.9% lost[b]	RR: 0.99 (0.70-1.39)[a]
				Women	1,403	≥10% lost vs. 0-4.9% lost[b]	RR: 0.47 (0.32-0.68)[a]
						5-9.9% lost vs. 0-4.9% lost[b]	RR: 0.75 (0.46-1.23)[a]
						0-4.9% gained vs. 0-4.9% lost[b]	RR: 0.88 (0.54-1.43)[a]
						≥5% gained vs. 0-4.9% lost[b]	RR: 0.70 (0.46-1.05)[a]

a Value or definition inverted from published results. b Weight difference percentage between age 70 and 75 years.

Education

The relationship between education and longevity was assessed in four studies (Table 4) (16, 18, 26, 31). One study of the FHS compared participants who received a college education or higher with lower educated participants (16). They did not find a significant association between educational level and reaching longevity. Another study in the HHP cohort also found no significant association when they compared men who graduated high school to less educated men on reaching longevity (85 years) (26). Two other studies, from the FHS cohort and the Rotterdam study, evaluated whether an increase per education level category might lead to a higher odds for reaching exceptional age (18, 31). The FHS study did find a significant OR of 1.25 (95% CI, 1.12-1.39) after adjustment for potential confounding factors (31), while the other did not (18).

Marital status
Two studies from the HHP investigated the association between unmarried men and the chance for reaching longevity (85 years), compared to married men (24, 26). Both studies found significant negative ORs of 0.64 (95% CI, 0.52-0.78) (26), and 0.44 (95% CI, 0.22-0.89) (24) (Table 4). In addition to marital status, the Rotterdam study investigated the association between spousal death and the odds for reaching 85 years of age (18). No significant associations between a deceased spouse and reaching longevity were found in men and women (Table 4) (18).

Table 4: Associations of education and marital status with longevity across studies.

Reference	Cohort	Age at baseline	Longevity cut-off point	Subgroup	n	Exposure contrast definition	Effect estimate + 95% CI
Education							
Goldberg, 1996	FHS	50	75	Men	723	College education or higher vs. lower	"No significant association"
							"No significant association"
				Women	953	College education or higher vs. lower	"No significant association"
							"No significant association"
Terry, 2005	FHS	40	85	-	1,445	One increase in category from not graduating high school, to graduating high school and then having education beyond high school	OR: 1.25 (1.12-1.39)
Willcox, 2006	HHP	45	85	Men	5,525	Graduating high school vs. less education (= <12 years)[1]	"No significant association"
Newson, 2010	Rotterdam	55	85	-	2,008	One increase in category (from primary education to university level)	"No significant association"
Marital Status							
Willcox, 2006	HHP	45	85	Men	5,525	Unmarried vs. married	OR: 0.64 (0.52-0.78)[a]
Bell, 2014	HHP	55	85	Men	1,292	Unmarried vs. married	OR: 0.44 (0.22-0.89)[a]
Newson, 2010	Rotterdam	72	85	-	2,008	Spousal death present vs. absent[a]	"No significant association"

aValue or definition inverted from published results.

Parental longevity and reproductive factors

We aimed to assess whether offspring of long-lived parents are long-lived as well, and whether this is mediated through the mother, the father or both (Table 5). Furthermore, we aimed to identify studies which investigated the association between reproductive factors and the chance of reaching longevity. We found one study which investigated the association of parental age at birth, and the number of siblings with longevity (Table 5) (25). No studies were found on other reproductive factors of interest, including the number of children, breast-feeding, age at menarche, and age at menopause in relation to longevity.

Parental longevity
Two studies, one within the FHS, and one within the IOWA-ESEPE, quantified parental longevity by looking if one, two or none of the parents reached the age of 75 or 85 years respectively. Both studies found that per one parent increase in longevity, the odds for reaching longevity in participants was increased, but only in women (16, 29). Two other studies investigated whether the mother's age and/or the father's age at death was associated with reaching longevity (20, 25). In the PAQUID study it was observed that only the mother's age at death was associated with longevity, but only in women (25). In the HHP they found that maternal longevity to at least 80 years was significantly associated with the chance for their male offspring to become a nonagenarian (OR 1.84, 95% CI 1.37-2.47) and/or centenarian (OR 2.26, 95% CI 1.04-4.90), compared to maternal survival until 60 years (20). No significant associations were found between paternal ages at death and offspring's longevity (20). Overall, these studies suggest that parental longevity is associated with reaching longevity, and that this association is primarily associated with maternal longevity. Whether parental longevity affects the chance of reaching longevity in both male and female offspring, remains unclear.

Parental age at birth and number of siblings
Only one study assessed the relationship between reproductive factors and longevity (25). In the PAQUID longevity study they assessed parental age at participant's birth separately for both biological parents in five years categories starting from below 25 years (reference group) to above 40 years (25). According to the authors, none of the comparisons yielded any significant associations between the parental age at birth and offspring longevity (Table 5). Although not necessarily a reproductive factor, the authors also assessed number of siblings and found no association in relation to longevity (25).

Table 5: Associations of parental longevity and reproductive factors with longevity across studies.

Reference	Cohort	Age at baseline	Longevity cut-off point	Subgroup	n	Exposure contrast definition	Effect estimate + 95% CI
Parental longevity							
Goldberg, 1996	FHS	50	75	Men	733	Per one parent increase in survival to 75 years	"No significant association"
				Women	946		OR: 1.39 (1.10-1.75)
Rantanen, 2012	HHP	56	80-89	Men	1,647	Maternal age at death	
						61-79 vs. ≤60	OR: 1.01 (0.78 – 1.31)
						≥80 vs. ≤60	OR: 1.18 (0.92 – 1.52)
						Paternal age at death	"No significant association"
			90-99	Men	1,346	Maternal age at death	
						61-79 vs. ≤60	OR: 1.30 (0.96 – 1.76)
						≥80 vs. ≤60	OR: 1.84 (1.37 – 2.47)
						Paternal age at death	"No significant association"
			100	Men	848	Maternal age at death	
						61-79 vs. ≤60	OR: 0.82 (0.33 – 2.05)
						≥80 vs. ≤60	OR: 2.26 (1.04 – 4.90)
						Paternal age at death	"No significant association"
Edjolo, 2013	PAQUID	70	90	Men	1,060	Maternal age at death	"No significant associations"
						Paternal age at death	"No significant association"
				Women	1,580	Maternal age at death	
						≥85 vs. <65[a]	HR: 1.36 (1.17-1.58)
						≥85vs. 65-79[a]	HR: 1.32 (1.11-1.57)
						≥85 vs. 80-84[a]	HR: 1.15 (0.98-1.35)
						Paternal age at death	"No significant association"
Dutta, 2011	Iowa-ESEPE	65	94	Men	1,092	One parent living ≥85 years vs Parents not living ≥85	OR: 1.22 (0.73-2.04)
						Two parents living ≥85 years vs Parents not living ≥85	OR: 1.16 (0.45-2.98)
		65	97	Women	1,698	One parent living ≥85 years vs Parents not living ≥85	OR: 1.80 (1.20-2.74)
						Two parents living ≥85 years vs Parents not living ≥85	OR: 2.44 (1.48-4.01)

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Parental age at participant's birth and number of siblings							
Edjolo, 2013	PAQUID	70	90	Men	1,060	Maternal age at participant's birth	"No significant association"
						Paternal age at participant's birth	"No significant association"
						1-5 siblings vs 0 siblings	"No significant association"
						>6 siblings vs. 0 siblings	"No significant association"
				Women	1,580	Maternal age at participant's birth	"No significant association"
						Paternal age at participant's birth	"No significant association"
						1-5 siblings vs 0 siblings	"No significant association"
						>6 siblings vs. 0 siblings	"No significant association"

aValue or definition inverted from published results.

Discussion

This review aimed to summarize the available evidence on the association of lifestyle, parental and reproductive factors with reaching longevity (defined as reaching a certain age) from cohort studies. Based on the presented results for lifestyle factors with longevity, smoking status and physical activity seem to be the most important factors that are associated with longevity, whereas alcohol intake, BMI, marital status and educational level show limited and/or contradictory associations. Furthermore, parental longevity seems to be significantly associated with reaching longevity, primarily through maternal longevity, and some studies indicate a stronger effect of parental longevity in female offspring compared to male offspring (16, 20, 25). Only one study investigated trends in effect estimates due to differences in the longevity cut-off age (20). They found that the association of smoking and parental longevity with longevity became stronger the higher the longevity cut-off age was. Other main findings of this review are the limited number of available studies (n=13) investigating lifestyle, and parental factors on longevity using a defined cut-off age, and the sheer lack of data on dietary and reproductive factors on longevity. Furthermore, across these studies substantial heterogeneity in baseline and longevity cut-off ages was found. Therefore, conducting a formal meta-analysis was not possible.

Being an (ex) smoker appears to decrease the chance of survival to old ages compared to non-smokers. This association seems to strengthen with the number of cigarettes smoked per day (16, 28). Furthermore, the effect of smoking status becomes stronger the higher the longevity cut-off age is (20). In addition, it was observed that the association between smoking and longevity might be stronger in men, compared to women (25, 29). However, this observation is based on a limited number of studies. Therefore, this possible interaction should be further assessed in future studies. One study investigated the effect of quitting smoking after 50 years of age on longevity, and did not find a significant increase in the chance for reaching longevity (27). The potential beneficial effect of quitting smoking on longevity in older individuals should therefore be further evaluated.

Studies that investigated the relationship between alcohol consumption and longevity showed contradictory results (16, 19). Only the HHP cohort found a significantly

inverse association between alcohol consumption and reaching longevity (24, 26), while the other cohorts did not find any association. However, the HHP cohort is characterized by a specific study population, of Japanese-American men, who might be genetically more vulnerable to the effects of alcohol consumption compared to other populations caused by an unfavourable distribution of the ALDH2 allele in Asian populations (32). Furthermore, different standards were used for defining (high) alcohol consumption which also limits the comparability across these studies.

Physical activity seems to be strongly associated with reaching longevity even at a minimal level of intensity (17, 19, 20, 24, 25, 28). Furthermore, no linear dose-response relationship was found between increasing levels of physical activity and reaching longevity. This suggests that being physically active is more important than the actual quantity of physical activity (19). However, it should be noted that a lack of physical activity can also be a symptom of underlying health problems which by itself might lead to premature mortality. One study stratified for smoking status and found no significant association between physical activity and longevity in smokers, while it was found in non-smokers (28). This could be explained by a possible interaction between smoking and physical activity on reaching longevity, or by a lack of power in the smoking group.

BMI showed significant inverse associations with longevity in both extremes of the spectrum (<20 kg/m2 and >30 kg/m2) (19, 24, 28, 29). Furthermore, the association seemed to increase in the non-smoking population compared to the smoking population. Therefore, not stratifying for smoking could lead to an underestimation of the effect of BMI on reaching longevity. No differences were found across sexes. Unintentional weight loss, in addition to underweight (BMI<20 kg/m2), showed a significant negative association with reaching longevity (18, 30). This could be explained by disease-associated weight loss or the correlation between smoking and being underweight (33). Because of this, it would be particularly interesting to investigate whether weight loss in the elderly as an intervention would be helpful or harmful and in what way weight changes can affect longevity in healthy and/or non-smoking populations.

Education has often been associated with health benefits and was found to be predictive for unhealthy behaviours that are associated with an increased risk for mortality (34, 35). However, we found no clear evidence that educational level is independently associated with reaching longevity. Out of four studies, only one study found a significant association between a higher education level and a higher chance of reaching longevity (31). Being married is usually associated with health benefits, also in the elderly, even if only moderately (36). The reviewed studies also showed significant associations between marital status and reaching longevity (24, 26).

Parental longevity was significantly associated with the offspring's longevity. Furthermore, it was found that this association was primarily present for maternal longevity, and not for paternal longevity (20, 25), and more pronounced in female offspring (16, 25, 29). There is a lot of potential for further research to see whether these maternal or paternal differences are upheld across different studies, and which factors might contribute to these differences. The potential different outcomes in men and women with regard to parental longevity, is another interesting question and should be analysed more closely in future studies.

The lack of data on dietary and reproductive factors, and longevity was another remarkable result of this review. Dietary factors other than alcohol intake and coffee consumption were not found. This is surprising, because dietary restriction in animal subjects is often associated with longevity (37), and several studies have shown significant relationships between specific dietary patterns and mortality in humans (i.e. (38, 39)).

The lack of cohort studies on the association between reproductive factors and longevity, given the higher average life-expectancy of females, is also surprising. Only one study investigated parental age at birth on longevity, which yielded no significant association (25). Furthermore, there was one excluded case-control study identified during the review, which assessed the age of mothers and fathers at birth and the birth order on longevity (40). They found that, following adjustments, the only remaining predictor of the offspring's longevity, was if the mother was below the age of 25 when giving birth to the offspring. These parameters need to be further assessed, as the PAQUID cohort did not find any associations (25).

Studying longevity is challenging and faces limitations. A possible source of bias includes depletion of susceptibles. Depletion of susceptibles helps us understand why some factors could have an attenuated relationship to longevity the older the subject gets. Examples of this are smokers who have already reached an advanced age. Their susceptibility to adverse health outcomes might differ from smokers who have died at an earlier age. This is important to consider, as the association with longevity will probably vary using different longevity cut-off ages, as well as different baseline ages at which the exposure was measured. The problem of reverse causation arises as well. Some baseline characteristics might be explained by the participants' preclinical disease status. For example, a person who contracts a potentially lethal or chronic disease on a younger age, and who is therefore less likely to reach longevity, will simultaneously be less likely to be physically active. Therefore, causal conclusions cannot be drawn based on the presented results.

In addition to the limitations of longevity research, one can argue that our in- and exclusion criteria were restrictive. However, the presented studies already vary widely between themselves, so relaxing our in- and exclusion criteria would have made interpreting the results on longevity even more challenging. To tackle the complexity of longevity research, the effect of different longevity cut-off ages, as well as the effect of different (baseline) ages, would be very interesting to assess within one study, as this was very informative in the study of Rantanen et al. (20). Such approaches could allow us more to understand longevity within a life course setting. Even though studies with a long observation time are scarce for this specific topic, many longitudinal cohort studies, that were previously set up for other purposes, could be used to assess longevity, as mortality is usually integrated in the outcomes.

Many gaps of knowledge have been identified in this review. In general it is evident that more research is needed to address the gaps of interest, test consistency and deepen our understanding of this research area.

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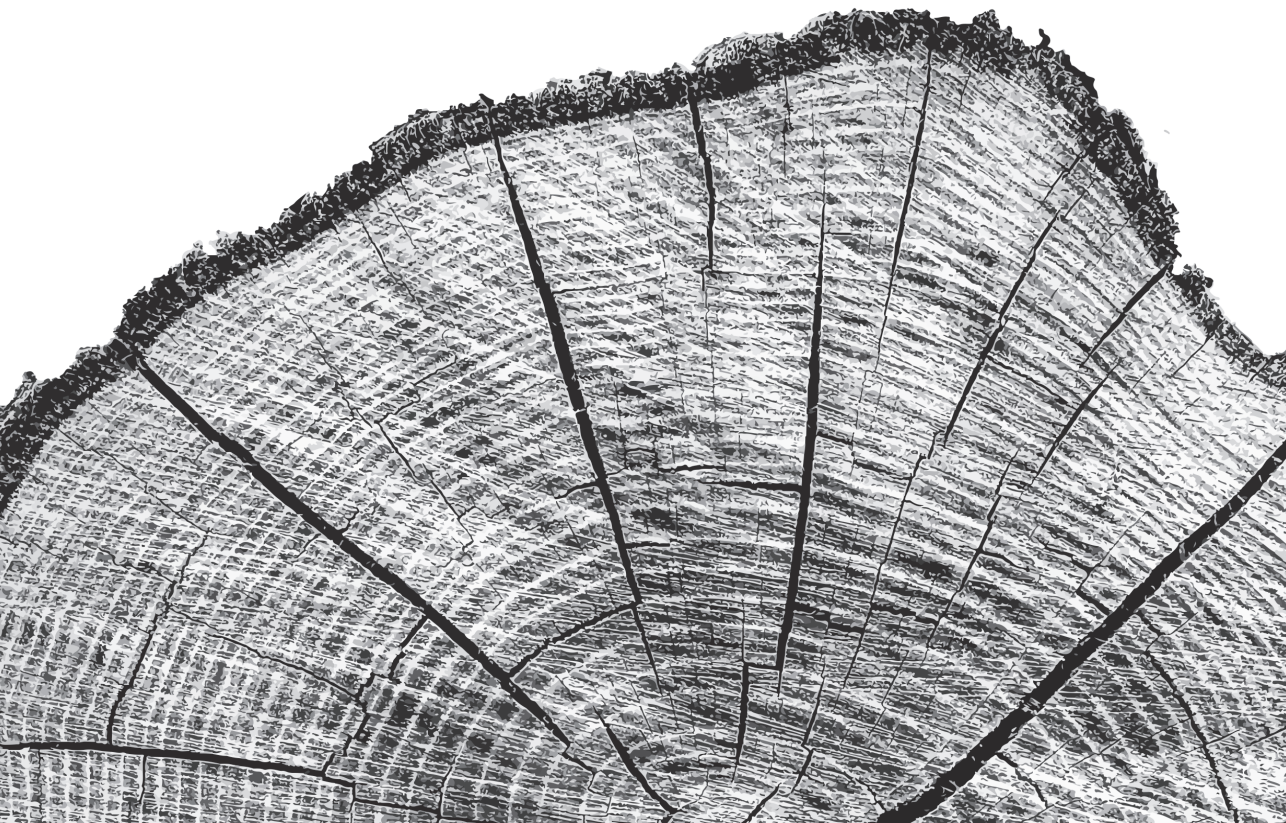
Parental longevity

Chapter 3

Parental lifespan and reaching longevity in the Netherlands Cohort Study (NLCS)

Lloyd Brandts, Frans W.A. van Poppel, and Piet A. van den Brandt

Submitted for publication



Parental lifespan and reaching longevity in the Netherlands Cohort Study (NLCS)

Lloyd Brandts, Frans W.A. van Poppel, Piet A. van den Brandt

Abstract

Background
Growing evidence suggests an association between parental longevity and lifespan of subsequent generations. We aimed to reproduce earlier findings, indicating a positive association between parental longevity and offspring's longevity. Additionally, we investigated whether this is mainly driven by the maternal or paternal germline in male and female offspring.
Methods
For these analyses, data from the oldest birth cohort (1916-17) of the Netherlands Cohort Study (NLCS) was used. 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. Multivariable-adjusted Cox regression analyses with a fixed follow-up time were based on 2,368 men and 2,657 women with complete parental survival data and relevant confounders to calculate Risk Ratios (RR) of reaching longevity.
Results
In age-adjusted models, paternal and maternal age at death were significantly positively associated with reaching 90 years in both male and female offspring. In male offspring, paternal age at death (≥90 years vs. <80 years) showed the strongest association with survival to 90 years (RR,1.42; 95% Confidence Interval (95%CI),1.07-1.89), after confounder correction. In female offspring, maternal age at death (≥90 years vs. <80 years) showed the strongest association with survival to 90 years (RR,1.20; 95%CI,1.04-1.40).
Conclusion
We observed that parental lifespan was associated with offspring reaching 90 years in both sexes. In male offspring, paternal survival showed stronger associations with longevity compared to maternal survival. In female offspring, maternal survival showed stronger associations with longevity compared to paternal survival.

Introduction

Several studies observed that parental longevity was significantly associated with the offspring's lifespan (1-6). Furthermore, it was found that this association was primarily present for maternal longevity, and not for paternal longevity (3, 4, 6), and also more pronounced in female offspring (1, 2, 4).
Using data from the Netherlands Cohort Study (NLCS) we aimed to reproduce earlier findings, indicating an association between parental longevity and offspring's longevity. Additionally, we aimed to investigate if these relationships differ by sex and whether it is mainly driven by the maternal and/or paternal germline in male and female offspring separately.

Methods

Population and study design

For this study data from the Netherlands Cohort Study (NLCS) was used. The NLCS was set up in September 1986 as a large prospective cohort study (7). Participants born in 1916 or 1917 were selected to form the longevity cohort for the current longevity analyses in the NLCS (i.e. aged 68-70 years at baseline), as has been done before in other NLCS longevity studies (8, 9). Follow-up for vital status of the longevity cohort until the age of 90 (2006-2007) was 99.9% complete. The date of death was collected by record linkage to the "Centraal Bureau voor Geneologie (CBG)" from 1986 until 1995, and the "gemeentelijke bevolkings administratie (GBA)". Seven participants were lost to follow-up due to migration before reaching the age of 90 years. As a result, this study population consisted of 3,646 men and 4,161 women.

Exposure assessment

At baseline, participants filled in an 11-page self-administered questionnaire on diet, lifestyle and other cancer risk factors, including information on paternal and maternal year of birth. Furthermore, they were asked in what year their mother and father had died and the cause of death. Parental age at death was computed by subtracting year of birth from year of death, for those parents who were deceased at baseline in 1986. Additional parental cause of death information was used to check whether the father and/or mother was still alive at baseline. Parental age at baseline was determined for parents who were still alive at baseline in September 1986.

Statistical analysis

Reaching the age of 90 years (yes/no) was used as our main outcome variable. For the analyses, maternal and paternal age at death were categorized as: <80, 80-<85, 85-<90, or $\geq$ 90 years. Participants whose natural father and/or mother were still alive at baseline, according to cause of death information, were only included in categorical analyses if the parental age was higher than 90 at baseline, to avoid misclassification of the exposure. Furthermore, parental longevity was defined as having a parent who belonged to the top 10% survivors of their birth cohort, using a dichotomous variable (yes/no). The sex- and birth cohort-specific parental longevity cut-off ages were based on national Dutch population-based survival tables (10).

Parental birth cohorts ranged from 1850-1906, with longevity cut-off ages ranging from 83-88 years in fathers, and from 84-93 years for mothers. Parental longevity was determined for the mother (yes, no), father (yes, no), and combined (none, only father, only mother, both).

Baseline characteristics are presented by offspring survival status using the mean with standard deviation (SD) for continuous variables, and using frequencies (N) and percentages (%) for categorical variables. Cross-tabulations were used to examine the distribution of environmental factors according to parental survival status. Age- and multivariable-adjusted risk ratios (RR) of reaching 90 years with 95% confidence intervals (95% CI) were estimated using Cox regression models with a fixed follow-up time (11, 12). Standard errors are calculated using the robust Huber-White sandwich estimator to account for underdispersion (13). Restricted cubic spline regression analyses were used for modeling continuous relationships between paternal and maternal age at death and the chance of reaching the age of 90 years. For these analyses, three knots were used at the 10th, 50th, and 90th percentile. The median ages at death of the reference category in categorical analyses were used as a reference in continuous analyses. Some additional sensitivity analyses were performed to assess the association between dichotomous exposure variables (parental survival to 85 years (yes/no), 90 years (yes/no) and survival to top 10% of their birth cohort (yes/no) and offspring survival to the age of 90 years.
Confounder selection was based on earlier studies studying parental longevity and offspring's longevity (1-4) and directed acyclic graphs (DAGs), using a disjunctive cause criterion approach (14). Confounders used for these analyses include: cigarette smoking status (never smoker/ former smoker/ current smoker), number of cigarettes smoked per day (continuous; centered), cigarette smoking duration (in years) (continuous; centered), alcohol consumption (<0.1, ≥0.1-5, >5-15, >15-30, and >30 g/day), non-occupational physical activity (≤30, >30-60, >60-90, >90 min/day), total energy intake (kcal; continuous), BMI at baseline (<18.5, ≥18.5-<25, ≥25-<30, and ≥30 kg/m2), educational level (primary/lower vocational education, junior/senior high school and higher vocational/university), marital status (never married/married/ divorced/widowed), number of (selected) diseases at baseline, and, depending on the exposure, mutually adjusted for paternal or maternal survival. Selected diseases at baseline include hypertension, heart attack, angina pectoris, stroke, any type of cancer excl. skin cancer, asthma, chronic bronchitis, and diabetes. All analyses were stratified by sex, and performed with STATA 15.0 (Statacorp. 2017. College Station, TX).

Results

Survival to the age of 90 years was more common in women (35.0%), compared to men (17.1%; Table 1). In men, those who survived to the age of 90 were more often a never smoker (15.8% vs. 8.9%), had a higher average non-occupational physical activity level (85.0 vs 72.4 min/day),more often had a higher vocational or university degree (25.3% vs. 17.2%), and were more often married (90.4% vs. 87.6%), compared to those who died before the age of 90. In women, we observed similar patterns, except for physical activity levels, which were comparable for both

survivors and non-survivors (56.0 vs. 55.9 min/day) (Table 1).
In male offspring, paternal age at death showed a significantly positive association with survival to the age of 90 in both age-adjusted (P-trend=0.002), and multivariable-adjusted analyses (P-trend=0.011; Table 3). In multivariable-adjusted analyses, males whose father died after the age of 90 years had a significantly higher chance of reaching the age of 90 years themselves (RR,1.42; 95%CI,1.07-1.89), compared to those whose father died before the age of 80 years. Compared to maternal age at death <80 years, maternal age at death ≥90 years was significantly positively associated with male offspring survival to 90 years in the age-adjusted model (RR,1.32; 95%CI,1.01-1.72), but not in the multivariable-adjusted model (RR,1.15; 95%CI,0.87-1.51). A significantly increased chance of reaching 90 was observed when only the father reached longevity (RR,1.30; 95%CI,1.02-1.65), and a somewhat weaker non-significantly increased chance when only the mother reached longevity (RR,1.16; 95%CI,0.88-1.42), compared to those of which none of the parents reached longevity. Having both parents reaching longevity was not associated with an increased chance of reaching the age of 90 years for male offspring (RR,1.04; 95%CI,0.63-1.73).

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

	Men		Women	
	Survived to age 90	Died before age 90	Survived to age 90	Died before age 90
n (%)	404 (17.1)	1,964 (82.9)	929 (35.0)	1,728 (65.0)
Year of Birth (%)				
1916	23.5	22.9	23.5	22.5
1917	76.5	77.1	76.5	77.5
Smoking status (%)				
Never smoker	15.8	8.9	74.5	69.2
Former smoker	56.2	50.5	15.3	16.2
Current smoker	28.0	40.6	10.2	14.6
Body Mass index (kg/m^2) (Mean ± SD)	24.7 ± 2.5	24.9 ± 2.7	24.9 ± 3.1	25.1 ± 3.7
Physical activity (min/day) (Mean ± SD)	85.0 ± 73.2	72.4 ± 59.5	56.0 ± 46.6	55.9 ± 50.0
Alcohol consumption (g/day) (Mean ± SD)	14.1 ± 14.8	13.8 ± 15.8	4.9 ± 8.2	4.7 ± 8.8
Total energy intake (kcal) (Mean ± SD)	2120 ± 469	2034 ± 448	1667 ± 369	1643 ± 368
Educational level (%)				
Primary/lower vocational	40.4	45.5	53.0	58.5
Junior/senior high school	34.4	37.4	37.7	33.3
Higher vocational/ university	25.3	17.2	9.4	8.2
Marital status (%)				
Married	90.4	87.6	59.3	56.3
Widow(er)	5.0	7.2	28.1	29.5
Divorced	2.0	2.1	3.3	3.2
Never married	2.7	3.2	9.3	11.1

Table 2: Baseline characteristics of the cohort members by survival status of parents in a birth cohort of 1916-17; Netherlands Cohort Study on diet and cancer (1986-2007).

	Male offspring				Female offspring			
Parental survival to top 10% of birth cohort	None	Only father	Only mother	Both	None	Only father	Only mother	Both
N (%)	1,552 (70.3)	334 (15.1)	254 (11.5)	68 (3.1)	1,803 (72.4)	334 (13.4)	290 (11.6)	64 (2.6)
Survived to 90 years (%)	15.6	20.7	19.3	19.1	33.6	38.3	39.3	42.2
Smoking status (%)								
Never Smoker	17.5	19.8	17.3	11.8	70.8	74.3	70.7	71.9
Former smoker	53.6	49.7	56.7	55.9	16.3	15.9	15.2	14.1
Current smoker	28.9	30.5	26.0	32.4	12.9	9.9	14.1	14.1
BMI(kg/m^2) (Mean ± SD)	24.8 ± 2.6	24.9 ± 2.9	24.7 ± 2.4	24.6 ± 2.6	25.1 ± 3.5	25.0 ± 3.4	24.9 ± 3.3	24.7 ± 3.1
Physical activity (min/day) (Mean ± SD)	74 ± 61	82 ± 73	70 ± 54	75 ± 62	56 ± 49	55 ± 47	57 ± 49	56 ± 52
Alcohol consumption (g/day) (Mean ± SD)	14.3 ± 16.2	11.9 ± 14.1	14.4 ± 14.7	12.4 ± 12.9	4.8 ± 8.6	4.5 ± 8.3	5.4 ± 9.3	4.1 ± 9.1
Total energy intake (kcal) (Mean ± SD)	2047 ± 451	2084 ± 454	2059 ± 456	1964 ± 362	1660 ± 371	1643 ± 367	1651 ± 358	1660 ± 390
Higher vocational/ University (%)	17.7	18.3	24.0	27.9	8.9	8.4	10.7	7.8
Married(%)	89.1	88.0	87.0	86.8	57.4	58.4	57.2	51.6

In female offspring, increasing paternal age at death was significantly positively associated with reaching longevity in the age-adjusted model (P-trend=0.007), but not in the multivariable-adjusted model (P-trend=0.069) (Table 3). Although not significant, paternal age at death ≥90 years pointed towards a positive association (RR,1.16; 95%CI,0.97-1.38) with offspring longevity in the multivariable-adjusted model, compared to paternal age at death <80 years (Table 3). Maternal age at death was significantly positively associated with reaching the age of 90 years in both the age-adjusted (P-trend=<0.001), and the multivariable-adjusted model (P-trend=0.003). In multivariable-adjusted analyses, women whose mother had died after the age of 90 had a significantly higher chance of reaching the age of 90 years (RR,1.20; 95%CI,1.04-1.40), compared to those whose mother died before the age of 80 years. Non-significant positive associations were observed with reaching the age of 90 years, for only father, only mother or both parents reaching longevity (Table 3).

Table 3: Age- and multivariable-adjusted RRs for reaching longevity according to parental survival in a birth cohort of 1916-17; Netherlands Cohort Study (1986-2007).

				Age-adjusted	Multivariable-adjusted [a]
	median	n	Survival	RR (95% CI)	RR (95% CI)
Male offspring					
Paternal age at death					
<80 years	69	1,392	208	Reference	Reference
80 - 84 years	82	404	78	1.29 (1.02-1.64)	1.28 (1.01-1.62)
85 - 89 years	87	298	55	1.23 (0.94-1.62)	1.16 (0.89-1.52)
≥90 years	92	213	48	1.51 (1.14-2.00)	1.42 (1.07-1.89)
P-trend				0.002	0.011
Maternal age at death					
<80 years	69	1,233	183	Reference	Reference
80 - 84 years	82	405	78	1.30 (1.02-1.65)	1.19 (0.94-1.51)
85 - 89 years	87	365	72	1.33 (1.04-1.70)	1.25 (0.97-1.60)
≥90 years	92	297	58	1.32 (1.01-1.72)	1.15 (0.87-1.51)
P-trend				0.007	0.112
Parental longevity (top 10% of birth cohort)					
None		1,551	242	Reference	Reference
Only father		334	69	1.33 (1.04-1.69)	1.30 (1.02-1.65)
Only mother		254	49	1.24 (0.94-1.63)	1.16 (0.88-1.42)
Both		68	13	1.22 (0.74-2.02)	1.04 (0.63-1.73)

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Female offspring					
Paternal age at death					
<80 years	69	1,653	549	Reference	Reference
80 - 84 years	82	423	157	1.12 (0.97-1.29)	1.10 (0.95-1.27)
85 - 89 years	87	304	115	1.14 (0.97-1.34)	1.07 (0.92-1.26)
≥90 years	92	216	88	1.23 (1.03-1.46)	1.16 (0.97-1.38)
P-trend				0.007	0.069
Maternal age at death					
<80 years	68	1,365	435	Reference	Reference
80 - 84 years	82	487	175	1.13 (0.98-1.30)	1.11 (0.96-1.28)
85 - 89 years	87	397	157	1.24 (1.07-1.43)	1.19 (1.03-1.37)
≥90 years	93	323	136	1.32 (1.14-1.53)	1.20 (1.04-1.40)
P-trend				<0.001	0.003
Parental longevity (top 10% of birth cohort)					
None		1,803	606	Reference	Reference
Only father		334	128	1.14 (0.98-1.33)	1.11 (0.96-1.29)
Only mother		290	114	1.17 (1.00-1.37)	1.11 (0.95-1.29)
Both		64	27	1.25 (0.94-1.68)	1.10 (0.34-1.47)

a Model adjusted for cigarette smoking status (never, former, current), cigarette smoking quantity (continuous, centered), cigarette smoking duration (continuous, centered), non-occupational physical activity (≤30 min, >30-60, >60-90, >90 min/day), Body Mass Index (<18.5, ≥18.5-<25, ≥25-<30, and ≥30 kg/m2), alcohol consumption (<0.1, ≥0.1-5, >5-15, >15-30, and >30 g/day), educational level (primary/lower vocational education, junior/senior high school and higher vocational/university), total energy intake (kcal; continuous), marital status (never married, married, widowed, divorced), number of (selected) diseases at baseline (0, 1, 2, 3 or more), and mutually adjusted for paternal or maternal survival.

Restricted cubic spline analyses indicated a positive association between paternal and maternal age at death and reaching age 90 in both male and female offspring (Figure 1). All figures showed a gradually increasing slope from the age of death ≥73 years, with steeper and statistically significant slopes observed for paternal age at death in men, and maternal age at death in women.

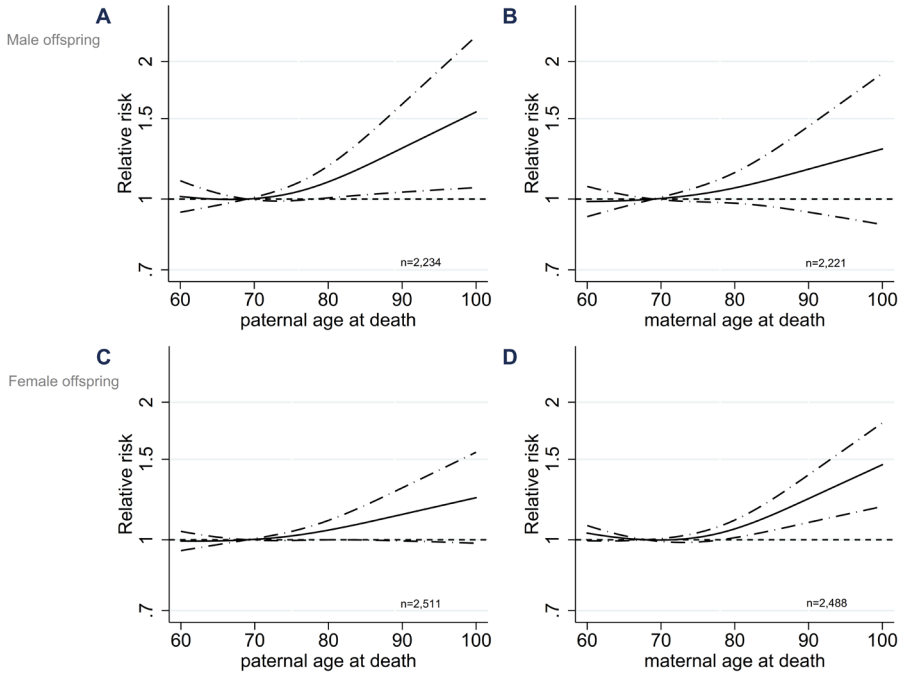

Figure 1: Nonparametric regression curve for the association between paternal and maternal age at death, and the chance of reaching 90 years in men and women. Solid line represents point estimate and dashed lines represent 95% confidence intervals. All models were adjusted for age (years), cigarette smoking status (never, former, current), cigarette smoking quantity (continuous, centered), cigarette smoking duration (continuous, centered), non-occupational physical activity (≤30 min, >30-60, >60-90, >90 min/day), Body Mass Index (<18.5, ≥18.5-<25, ≥25-<30, and ≥30 kg/m2), alcohol consumption (<0.1, ≥0.1-5, >5-15, >15-30, and >30 g/day), educational level (primary/lower vocational education, junior/senior high school and higher vocational/university), total energy intake (kcal; continuous), marital status (never married, married, widowed, divorced), number of (selected) diseases at baseline (0, 1, 2, 3 or more), and mutually adjusted for paternal or maternal survival, (A) P- nonlinearity=0.069. (B) P- nonlinearity=0.418. (C) P- nonlinearity=0.236. (D) P-nonlinearity=0.001.

In sensitivity analyses, the strongest association (RR,1.33; 95%CI, 1.01-1.76) with male offspring survival to 90 years was observed with paternal survival to age 90 years (Table 4). In female offspring maternal survival to age 85 years showed the strongest association with survival to age 90 (RR,1.16; 95%CI,1.04-1.30). Weaker, non-significant associations were observed at higher maternal survival cut-off ages (Table 4).

Table 4: Age- and multivariable-adjusted RRs for reaching 90 years according to parental survival to age 85 and 90 years, and top 10% survival of their birth cohort; Netherlands Cohort Study (1986-2007).

	Male offspring				Female Offspring			
			Age-adjusted	Multivariable-adjusted [a]			Age-adjusted	Multivariable-adjusted [a]
	n	Survival	RR (95% CI)	RR (95% CI)	n	Survival	RR (95% CI)	RR (95% CI)
Paternal survival to top 10% of their birth cohort								
No	1,867	302	Reference	Reference	2,160	740	Reference	Reference
Yes	413	83	1.24 (1.00-1.55)	1.22 (0.98-1.52)	410	161	1.15 (1.00-1.31)	1.09 (0.95-1.25)
Maternal survival to top 10% of their birth cohort								
No	1,938	323	Reference	Reference	2,187	748	Reference	Reference
Yes	332	66	1.19 (0.94-1.51)	1.07 (0.83-1.36)	359	143	1.16 (1.01-1.34)	1.08 (0.94-1.24)
Paternal survival to 85 years								
No	1,796	286	Reference	Reference	2,078	707	Reference	Reference
Yes	511	103	1.27 (1.03-1.55)	1.20 (0.98-1.47)	520	203	1.15 (1.01-1.30)	1.08 (0.96-1.22)
Maternal survival to 85 years								
No	1,638	216	Reference	Reference	1,852	610	Reference	Reference
Yes	662	130	1.23 (1.02-1.49)	1.14 (0.94-1.38)	720	293	1.24 (1.11-1.38)	1.16 (1.04-1.30)
Paternal survival to 90 years								
No	2,093	341	Reference	Reference	2,382	822	Reference	Reference
Yes	213	48	1.39 (1.06-1.81)	1.33 (1.01-1.76)	216	88	1.18 (1.00-1.40)	1.12 (0.94-1.32)

Maternal survival to 90 years								
No	1,999	331	Reference	Reference	2,249	768	Reference	Reference
Yes	302	60	1.20 (0.94-1.54)	1.07 (0.83-1.37)	324	136	1.23 (1.07-1.41)	1.13 (0.99-1.30)

a Model adjusted for cigarette smoking status (never, former, current), cigarette smoking quantity (continuous, centered), cigarette smoking duration (continuous, centered), non-occupational physical activity (≤30 min, >30-60, >60-90, >90 min/day), Body Mass Index (<18.5, ≥18.5-<25, ≥25-<30, and ≥30 kg/m2), alcohol consumption (<0.1, ≥0.1-5, >5-15, >15-30, and >30 g/day), educational level (primary/lower vocational education, junior/senior high school and higher vocational/university), total energy intake (kcal; continuous), marital status (never married, married, widowed, divorced), number of (selected) diseases at baseline (0, 1, 2, 3 or more), and mutually adjusted for paternal or maternal survival.

Discussion

In this large prospective cohort study, we observed that parental survival to ages 80 year and older pointed towards an increasing likelihood of reaching the age of 90 years in both male and female offspring, compared to parental age at death before 80 years, in age-adjusted analyses. After further adjustment for offspring environmental factors and disease history, paternal survival in male offspring and maternal survival in female offspring in particular, were still significantly positively associated with an increased likelihood of reaching the age of 90 years.
Several studies have investigated the parent-offspring heritability of longevity with varying study designs and results. Most studies used cross-sectional analyses comparing multiple cohorts, or cases to younger controls using historical genealogical data (e.g. (15-17)), as summarized in (18). Of these, parental lifespan showed positive associations with offspring lifespan in all twelve studies investigating this relationship (18). When looking at patterns of inheritance, most evidence was observed for the presence of a mother-daughter longevity relationship (positive association, N=13; no association, N=3), and least evidence for a father-daughter relationship (positive association, N=6; no association, N=10)(18).
Similar to our study, several studies have used a prospective cohort design to study the parent-offspring longevity relationship (1-5). Three studies observed no significant association between parental age and death and male offspring longevity after confounder adjustment (1, 2, 4). In analyses from the Honolulu Heart Program (HHP), a significant association was observed between maternal age at death ≥80 years and male offspring survival to 90 (OR,1.84; 95%CI,1.37-2.47), and 100 years (OR,2.26; 95%CI,1.04-4.90), respectively(3), but not for paternal age at death. However, the effect estimates were not shown(3).

Regarding female offspring, in the PAQUID study, women had a significantly increased chance of reaching the age of 90 years if their mother had reached the age of 85 years, compared to maternal age at death between 65-79 years (4). No association was observed with paternal age at death. In analyses from the Women's Health Initiative, both maternal and paternal age at death ≥90 years were significantly associated with an increased odds of reaching the age of 90 years, compared to maternal or paternal survival to age <70 years (5).

Based on the existing literature and the results of our age-adjusted analyses, an older age at death of the parents seems to increase the likelihood of reaching old age in offspring. However, the observed relationship between parental longevity and offspring longevity is probably no direct causal relationship. The survival advantage of parents is most likely transferred to their offspring by a combined effect of behavioral, environmental, and genetic influences, as proposed in Figure 2.

Behavioral and environmental factors of the offspring and their parents might differ due to historical contexts in which the generations have lived. However, (socio-economic) childhood conditions have been associated with attained educational level and the development of several diseases (19), but also with lifestyle characteristics including BMI level, alcohol consumption and smoking behavior in adulthood (20).

Therefore, we hypothesize that offspring environmental and behavioral factors might partially act as a proxy for parental characteristics that could have contributed to a longevity advantage. When adjusting for several offspring behavioral/environmental factors and history of (selected) diseases, the causal pathways "A" and "C" become partially blocked.

In the multivariable-adjusted analyses, we observed that the father-son and mother-daughter longevity relationship showed somewhat stronger and significant effect estimates, compared to the effect estimates of the mother-son and father-daughter longevity relationship. This could imply that genetic-, or residual confounding factors of the "A" and "C" pathway, have a more prominent role in the heritability of old age survival between fathers and sons, and mothers and daughters.

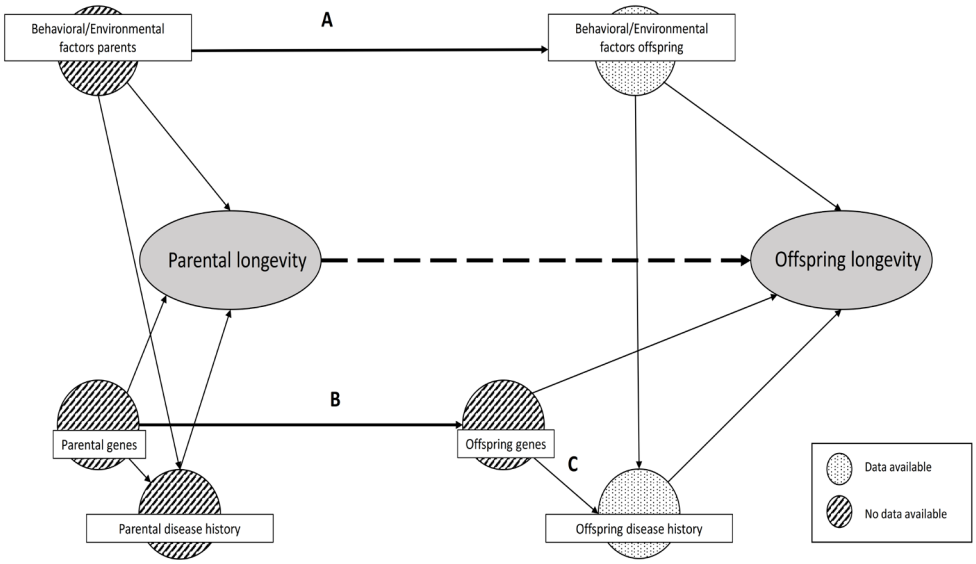

Figure 2: A simplified conceptual representation of the relationship between parental longevity and offspring longevity.

Other prospective cohort studies observed no significant father-son longevity relationship (3, 4), however no effect estimates were shown. Among the above mentioned genealogical studies, eight observed a father-son longevity association, while an equal number (N=8) observed no association. Therefore, more studies are needed to investigate whether our findings can be replicated in other cohorts as well.

More consistent evidence exists for a mother-daughter longevity relationship (e.g. (4, 5, 18)). While a direct causal relationship seems unlikely, as proposed in Figure 2, it would be interesting to investigate which underlying environmental and/or genetic factors may contribute to this observed association.

In analyses of the Framingham study, an increased odds of reaching the age of 75 was observed per one parent increase in survival to 75 years (1). In the Iowa-ESEPE study, women were more likely to reach the age of 97 years when one or both parents survived to the age of 85 years, compared to none of the parents surviving to 85 years (2). In the WHI, both parents surviving to 90 years was associated with an increased odds of reaching 90 years in female offspring(5). We did not observe an additional increased chance of reaching 90 years when both parents reached longevity in both men and women. However, the absolute number of participants of which both parents reached longevity was very small, which makes it difficult to draw any conclusions based on this finding. We also observed a notably higher percentage of current smokers in these specific groups, which might have also altered our results (Table 2).

Strengths of this study are the prospective study design, which limits the risk for selection, and information bias, and the detailed information collected on confounding factors. Furthermore, the study population was very homogenous with respect to age, making confounding by age unlikely.
There were some limitations to our study. Firstly, the men and women included for our analyses have already survived to an advanced age, which might have led to survivorship bias. Secondly, only limited information on parental vital status was available for participants with missing data on parental age at death, including those whose parents were still alive at baseline. Because these parents most likely survived to older ages, this might have led to a higher drop-out of participants whose parents survived to advanced ages. Finally, all causes of death of the parents and offspring were taken into account for these analyses, instead of natural causes of death only. These biases might have led to an underestimation of the true relationship between parental lifespan and offspring lifespan.

In conclusion, we observed that paternal age at death was significantly positively associated with reaching the age of 90 years in men, and maternal age at death was significantly positively associated with reaching the age of 90 years in women. Weaker, non-significantly, positive associations were observed between maternal age at death and reaching 90 years in male offspring, and between paternal age at death and reaching 90 years in female offspring. Regarding parental longevity, paternal longevity showed the strongest association with reaching the age of 90 years in male offspring.

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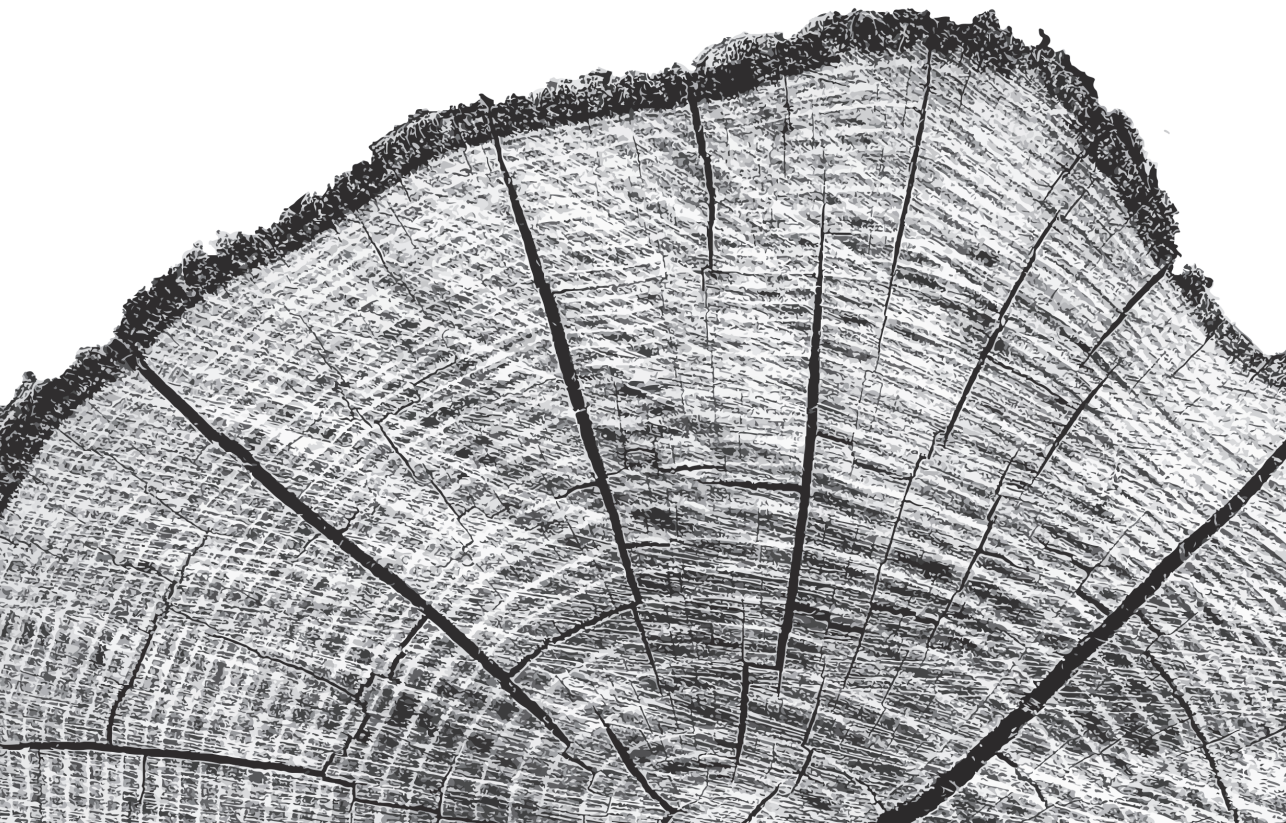
Lifestyle

Chapter 4

Sex-specific associations between smoking habits and reaching longevity: Netherlands Cohort Study

Lloyd Brandts, and Piet A. van den Brandt

Geriatr Gerontol Int. July 2018; 18: 1249-1258



Sex-specific associations between smoking habits and reaching longevity: Netherlands Cohort Study

Lloyd Brandts, Piet A. van den Brandt

Abstract

Aim

Tobacco smoking has been found to be significantly associated with a decreased chance of reaching longevity in men, but not in women. Furthermore, it is still unclear how the association of smoking status with longevity varies under the influence of underlying smoking characteristics. Therefore, we aimed to quantify the association between several smoking characteristics and the chance of reaching the age of 90 years in men and women separately.

Methods

We conducted a prospective cohort study among the oldest birth cohorts (1916-1917) of the Netherlands Cohort Study, who completed a baseline questionnaire in 1986 (at ages 68-70), and had complete vital status information until 90 years of age (2006-2007, n=7,807). Multivariable-adjusted analyses were based on 6,642 men and women, of which 16.0 and 34.3 percent reached longevity, respectively.

Results

The relationship of smoking status with longevity was stronger in men than in women (current vs. never smokers; Risk Ratio (RR), 0.44; 95%CI, 0.34-0.56 in men, and RR, 0.67; 95%CI, 0.57-0.79 in women). Furthermore, significantly inverse associations were found between longevity and increasing cigarette smoking quantity, duration, and tar and nicotine exposure, which partially explain the observed difference between both sexes. Quitting smoking significantly increased the chance of reaching longevity compared to current smokers.

Conclusions

The effect of smoking status on reaching longevity seemed stronger in men compared to women, which can be partially explained by differences in smoking habits. Never smokers had the highest chance of reaching 90 years of age in both sexes.

Introduction

Surviving to the age of 90 years is a phenomenon that only a small part of the population has been able to reach. To date, tobacco smoking is one of few established lifestyle factors associated with a decreased chance of reaching an old age, commonly referred to as longevity (1-11). Although most studies found a significant negative association between tobacco smoking and reaching longevity in men, inconclusive results were found in women (1, 9, 11). Additionally, besides smoking status little is known on how specific smoking characteristics relate to the chance of reaching longevity.

Using a large prospective cohort, we examined whether overall- and tobacco specific smoking status) at the age 68-70 years was associated with an increased or decreased chance of reaching longevity, defined as reaching 90 years of age in both sexes separately. In addition, we assessed which, if any, (early) cigarette smoking features, such as smoking quantity, duration, age at smoking initiation and cessation, inhalation, filter-tip usage, and the amount of tar and nicotine exposure were associated with reaching longevity.

Methods

Study design and population

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, which aimed to investigate the relationship between diet and cancer in the Netherlands (12). Baseline data were collected from 120,852 men and women on lifestyle, dietary habits and other cancer risk factors using a self-administered questionnaire. Generally, the NLCS uses a case-cohort design with a random subcohort of 5,000 participants to increase efficiency in the data processing and follow-up (13). In addition, the full NLCS 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. Because only a part of the subcohort was “at risk” to reach the age of 90 years at the onset of this longevity project, we were forced to look beyond the subcohort and select those participants in the full cohort who were able to reach the age of 90 years in 2007. Therefore, the data entry was restricted to the oldest birth cohorts (1916, and 1917) of the NLCS cohort. The participants from these two birth years form the longevity cohort for the current analyses in the NLCS (i.e. aged 68-70 years at baseline).

Follow-up for vital status of the longevity cohort until the age of 90 (2006-2007) was 99.9% complete. Seven participants were lost to follow-up due to migration. As a result, this study population consisted of 3,646 men and 4,161 women (Figure 1). The NLCS study has been approved by the institutional review boards of Maastricht University (Maastricht, Netherlands) and the Netherlands Organisation for Applied Scientific Research TNO (Zeist, Netherlands).

Exposure assessment
At baseline, all participants completed an 11-page self-administered questionnaire, including detailed information on tobacco consumption. Besides smoking status (never, former, and current smoker), participants were asked about their starting age, quitting age, smoking quantity, -duration and smoke inhalation for each tobacco product separately. Additional information was asked about specific cigarette characteristics like brand, filter usage, and type of cigarette (mild, regular, and strong)(14). Cigarette brand-specific information on nicotine (in mg) and tar content (in mg) was obtained from the Dutch Inspectorate for Health Protection, the Dutch Foundation on Smoking and Health, and the Dutch Foundation of the Tobacco Industry(14). The product of cigarette smoking quantity and cigarette brand-specific content was used to calculate the exposure to tar and nicotine per day. Questionnaire data used of the birth cohorts 1916-1917 were key-entered and processed in a standardized manner, and blinded with respect to the outcome. Participants with missing information on overall tobacco smoking status (n=37), and potential confounders were excluded from the analyses (n=1,275). As a result, 3,283 (49.4%) men and 3,359 (50.6%) women were included in the analyses (Figure 1).

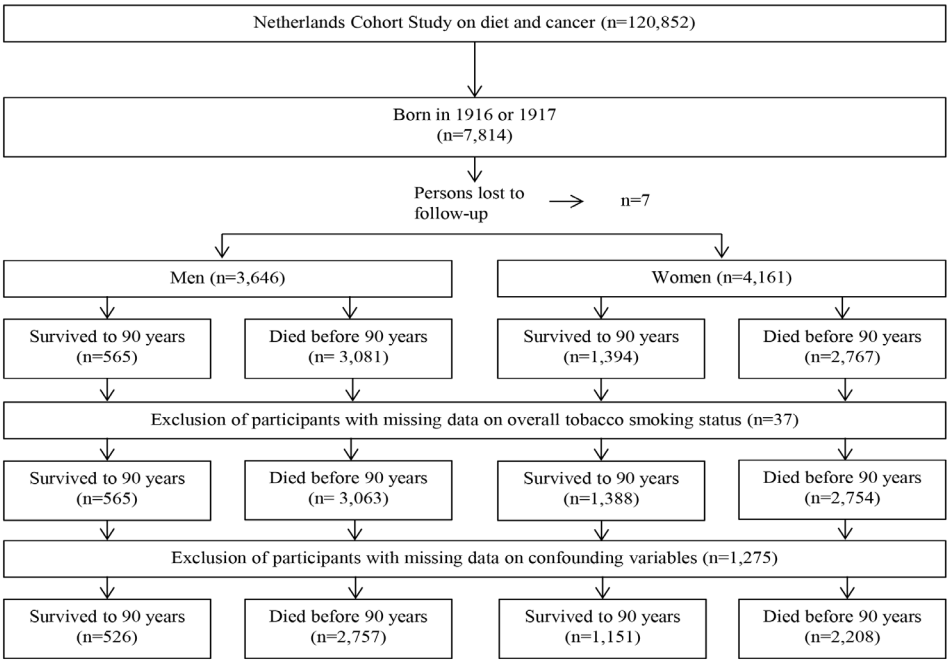


Figure 1: Flow diagram of the number of cohort members included for the analyses on smoking and longevity.

Statistical Analyses
Baseline characteristics were presented by gender, and overall tobacco smoking status with frequencies (percentages) for categorical variables, and with mean

including SD for continuous variables. Investigated smoking habits included, overall and tobacco specific (cigarette, cigar, and pipe) smoking status, cigarette smoking quantity, cigarette smoking duration, age at cigarette smoking initiation, age at cigarette smoking cessation, time since cigarette smoking cessation, cigarette smoke inhalation, filter-tip usage, and exposure to tar and nicotine.

Age- and multivariable-adjusted Risk Ratios(RR) of reaching longevity with corresponding 95% confidence intervals (95%CI) were estimated using Cox regression models with a fixed follow-up time(15, 16). Standard errors were calculated using the robust Huber-White sandwich estimator to account for underdispersion(17). All analyses were performed separately for men and women. In multivariable analyses, RRs were adjusted for potential confounders. Diseases for which we adjusted had the potential to influence smoking habits, and the chance of reaching longevity. These included any type of cancer, asthma, chronic bronchitis, angina pectoris, heart attack, stroke and diabetes. For trend-analyses, ordinal exposure variables were fitted as continuous terms, and never cigarette smokers were excluded. To evaluate potential effect-modification, multivariable-adjusted analyses of cigarette smoking status with longevity were performed within strata of important risk factors. Wald-tests and cross-product terms were used to test for interaction with these factors. All analyses were performed using Stata 14.0 (StataCorp. 2015. College Station). P-values were based on two-sided tests and considered statistically significant if $P < 0.05$.

Results

Compared to women, men were more likely to be an ever smoker of any tobacco product at baseline (Table 1). Most smokers exclusively smoked cigarettes, especially in women. In general, the average number of cigarettes smoked per day, and years of smoking duration was higher in men compared to women (Table 1). Among ever cigarette smokers, men were more likely to inhale smoke, and less likely to smoke filter-tipped cigarettes than women (Table 1).

In men, smokers were less often highly-educated compared to never smokers (Table 1). In women, smokers had a somewhat lower average BMI, and were more often highly-educated compared to never smokers. In both sexes, the mean alcohol consumption per day was highest in smokers, and the proportion of people with a history of (selected) diseases at baseline was highest in former smokers (Table 1).

Overall, men were less likely to reach the age of 90 years compared to women (16.0% vs 34.3%). The proportion of people who have reached the age of 90 years was higher in never smokers, compared to former and current smokers for both men (25.6% vs. 18.2% and 11.4%, respectively) and women (36.5% vs. 32.4% and 26.1%, respectively) (Table 1).

Table 1: Baseline characteristics of the cohort members by gender and overall tobacco smoking status in birth cohorts of 1916-17; Netherlands Cohort Study on diet and cancer (1986-2007).

Baseline characteristics	Men			Women		
	Never smoker	Former smoker	Current smoker	Never smoker	Former smoker	Current smoker
n (%)	305 (9.3)	1,605 (48.9)	1,373 (41.8)	2,314 (68.9)	550 (16.4)	495 (14.7)
Use of tobacco products, %						
Ever cigarette smokers[a]	NA	59.5	49.5	NA	99.6	98.0
Ever cigar smokers[a]	NA	2.6	5.5	NA	0.2	0.6
Ever pipe smokers[a]	NA	0.4	2.0	NA	0	0
Ever cigar and pipe smoker[a]	NA	1.2	2.8	NA	0	0
Ever cigarette & other type of tobacco smoker	NA	36.3	40.2	NA	0.2	1.4
Smoking characteristics[b], mean ± SD						
Exclusively cigarette smokers[a]						
Number of cigarettes smoked per day	NA	17.8 ± 11.8	15.4 ± 8.6	NA	8.8 ± 9.0	12.1 ± 8.2
Cigarette smoking duration (y)	NA	35.0 ± 11.1	50.4 ± 5.9	NA	22.9 ± 12.9	37.2 ± 12.9
Age at cigarette smoking initiation (y)	NA	17.6 ± 4.2	17.1 ± 4.4	NA	27.3 ± 10.2	28.6 ± 11.9
Age at cigarette smoking cessation (y)	NA	54.2 ± 10.2	NA	NA	53.1 ± 12.6	NA
Cigarette smoke inhalation, % yes	NA	76.5	74.4	NA	32.9	41.8
Filter-tipped cigarettes, % yes	NA	20.0	36.4	NA	70.5	79.9
Type of cigarette, n (%)						
Mild	NA	32.8	22.9	NA	56.4	55.4
Regular	NA	54.8	59.5	NA	30.7	32.9
Strong	NA	11.4	16.2	NA	0.7	1.5
Tar (mg/d)	NA	368.1± 263.8	318.8± 206.0	NA	123.7± 135.3	154.5± 140.8
Nicotine (mg/d)	NA	31.2 ± 29.2	28.1 ± 24.0	NA	9.4 ± 10.3	12.1 ± 11.1
Exclusively cigar smokers[a]						

Number of cigars smoked per day	NA	4.0 ± 2.6	4.2 ± 3.3	NA	NA	NA
Cigar smoking duration (in years)	NA	30.8 ± 12.6	44.5 ± 10.3	NA	NA	NA
Exclusively pipe smokers[a]						
Number of pipes smoked per day	NA	5.3 ± 3.4	8.8 ± 8.7	NA	NA	NA
Pipe smoking duration (in years)	NA	35 ± 11.9	45.4 ± 10.5	NA	NA	NA
Non-smoking characteristics						
Year of birth, %						
1916	20.0	23.6	23.8	24.3	22.4	19.4
1917	80.0	76.5	76.2	75.7	77.6	80.6
Body Mass Index (kg/m^2), mean ± SD	24.8 ± 2.8	25.1 ± 2.6	24.6 ± 2.8	25.3 ± 3.6	25.0 ± 3.4	24.2 ± 3.4
Non-occupational physical activity (min/day), mean ± SD	72.0 ± 62.4	72.6 ± 59.9	72.3 ± 65.2	55.2 ± 50.0	54.0 ± 42.3	54.0 ± 45.4
Educational level, %						
Higher vocational education/ university	21.6	15.6	16.0	6.9	11.5	8.9
Alcohol consumption, mean ± SD	6.0 ± 9.7	13.3 ± 14.6	15.3 ± 16.8	3.1 ± 6.0	7.8 ± 9.8	10.2 ± 14.3
History of (selected) diseases[c], %	29.8	43.0	32.8	27.4	32.2	24.8
Survival status						
Survived to the age of 90 years, %	25.6	18.2	11.4	36.5	32.4	26.1

a Smokers of other tobacco products not included. b Number of participants used may vary from the study population due to missing values on specific exposure variables. c Diseases included; diseases that had the potential to influence smoking habits, and the chance of reaching longevity including any type of cancer, diabetes, asthma, bronchitis, heart attack, angina pectoris, and cerebral hemorrhage.

As shown in Table 2, male tobacco smokers had a significantly decreased chance of reaching longevity, compared to never smokers (RR, 0.44; 95%CI, 0.34-0.56 and RR 0.76; 95%CI, 0.61-0.95 for current and former smokers, respectively) after adjustment for selected confounders. In tobacco-specific multivariable-adjusted analyses, male current cigarette smokers had a significantly decreased chance of reaching longevity compared to never smokers (RR, 0.37; 95%CI, 0.27-0.50). After additional adjustments for cigarette smoking quantity and –duration, the effect estimate between cigarette smoking status and longevity was somewhat weaker (RR, 0.47; 95%CI, 0.33-0.66). Current cigar smokers had a significantly decreased chance of reaching longevity, compared to never smokers (RR, 0.48; 95%CI, 0.25-0.90. Because the number of exclusively pipe smokers was small, we combined cigar and pipe smokers. In these analyses current cigar and/or pipe smokers had a significantly decreased chance of reaching longevity compared to never smokers (RR, 0.48; 95%CI, 0.29-0.77). Men who were current cigarette smoker and current cigar and/or pipe smoker also showed a significantly decreased chance of reaching longevity, compared to never smokers (RR, 0.41; 95%CI, 0.28-0.60; Table 2).

In women, current and former cigarette smokers had a decreased chance of reaching longevity compared to never smokers (RR, 0.67; 95%CI, 0.57-0.78, and RR 0.85; 95%CI, 0.75-0.98, respectively), After additional adjustment for cigarette smoking quantity and duration, the association with longevity became somewhat stronger for currently cigarette smoking women (RR, 0.61; 95%CI, 0.52-0.73;Table 2). After adjustment for cigarette smoking quantity and –duration, gender still acted as a significant effect-modifier (P-interaction=0.040).

Table 2: Age- and multivariable-adjusted RRs for reaching longevity according to overall and tobacco specific smoking status in birth cohorts of 1916-17; Netherlands Cohort Study (1986-2007).

	Men				Women			
			Model 1[a]	Model 2[b]			Model 1[a]	Model 2[b]
	n	90+	RR[§] (95% CI)	RR[§] (95% CI)	n	90+	RR[§] (95% CI)	RR[§] (95% CI)
Tobacco smoking status								
Overall tobacco								
Never tobacco	305	78	1 (reference)	1 (reference)	2,314	844	1 (reference)	1 (reference)
Former	1,605	292	0.71 (0.57-0.88)	0.76 (0.61-0.95)	550	178	0.89 (0.78-1.01)	0.85 (0.74-0.97)
Current	1,373	156	0.44 (0.35-0.57)	0.44 (0.34-0.56)	495	129	0.71 (0.61-0.84)	0.67 (0.57-0.79)
P for trend			<0.001	<0.001			<0.001	<0.001
P-interaction$_{(sex)}$[b]								0.015
Exclusively cigarettes[c]								
Former	955	161	0.66 (0.52-0.84)	0.73 (0.57-0.94)	548	178	0.89 (0.78-1.02)	0.85 (0.75-0.98)
Current	679	63	0.36 (0.27-0.49)	0.37 (0.27-0.50)	485	125	0.71 (0.60-0.83)	0.67 (0.57-0.78)
P for trend			<0.001	<0.001			<0.001	<0.001
P-interaction$_{(sex)}$[b]								0.002
Exclusively cigarettes[c] (additionally adjusted for smoking quantity and duration)								
Former	900	156	0.64 (0.50-0.82)	0.68 (0.53-0.88)	497	161	0.72 (0.59-0.88)	0.70 (0.57-0.86)
Current	616	58	0.51 (0.36-0.71)	0.47 (0.33-0.66)	442	114	0.66 (0.55-0.78)	0.61 (0.52-0.73)
P for trend			<0.001	<0.001			<0.001	<0.001
P-interaction$_{(sex)}$[b]								0.040
Exclusively cigars[c]								
Former	42	10	0.92 (0.52-1.64)	1.07 (0.62-1.85)	1	0	NA	NA
Current	76	10	0.51 (0.28-0.94)	0.48 (0.25-0.90)	3	2	NA	NA

P for trend			0.031	0.026				
Exclusively cigar and/or pipe[c]								
Former	72	14	0.80 (0.48-1.32)	0.91 (0.55-1.49)	1	0	NA	NA
Current	137	18	0.50 (0.31-0.79)	0.48 (0.29-0.77)	3	2	NA	NA
P for trend			0.003	0.003				
Exclusively cigarettes with cigar and/or pipe[c]								
Former cigarette, former cigar and/or pipe	582	117	0.78 (0.61-1.01)	0.78 (0.60-1.00)	1	0	NA	NA
Former cigarette, current cigar and/or pipe	160	29	0.71 (0.48-1.04)	0.68 (0.46-1.01)	1	0	NA	NA
Current cigarette, former cigar and/or pipe	35	5	0.56 (0.24-1.28)	0.62 (0.28-1.41)	0	0	NA	NA
Current cigarette, current cigar and/or pipe	357	41	0.45 (0.32-0.64)	0.41 (0.28-0.60)	6	2	NA	NA

a Age adjusted model. b Model adjusted for age (years), body mass index (<18.5, 28.5-25, 25-<30, 30+ kg/m2), non-occupational physical activity (≤30/ >30-60/ >60-90/ >90 min/day), alcohol consumption (0, 0.1-15, >15 g/day), educational level (low, medium, high), and number of diseases at baseline (0,1,2,3 or more). c Using never tobacco smokers as a reference.

In multivariable-adjusted analyses among current smokers, increasing cigarette smoking quantity was significantly associated with a decreasing chance of reaching longevity, with Ptrend=0.006, and Ptrend=0.007 in men and women respectively (Table 3). Men and women who smoked more than 20 cigarettes per day, had a substantially lower chance of reaching longevity compared to never tobacco smokers (RR 0.29; 95%CI 0.14-0.58, and RR 0.49; 95%CI, 0.33-0.72, respectively). A non-significantly inverse dose-response relationship between smoking quantity and longevity was observed in former cigarette smokers of both sexes (Table 3).

Across increasing categories of smoking duration, a decreased chance of reaching longevity was observed among current smokers of both sexes (Table 3). In multivariable-adjusted analyses, currently smoking men and women who smoked over 50 years at baseline were substantially less likely to reach longevity compared to never smokers (RR, 0.33; 95%CI, 0.23-0.48, and RR, 0.62; 95%CI, 0.44-0.88, respectively). In former smokers an inverse trend across categories of smoking duration with reaching longevity was only observed in men (Ptrend<0.001). No significant associations were observed between age at smoking initiation and longevity in both sexes (Table 3).

In men, multivariable-adjusted analyses showed an increasing chance of reaching longevity with earlier ages at smoking cessation compared to current smokers (Table 4). Men who had quit smoking less than 5 years before baseline already had a significantly increased chance to reach longevity (RR, 1.60; 95%CI, 1.02-2.52) compared to current smokers at baseline. Although less strong than in men, an increasing chance of reaching longevity with earlier ages at smoking cessation was also observed in women (Ptrend=0.011).

In multivariable-adjusted analyses, whether or not subjects did inhale cigarette smoke (yes vs. no), or smoked filter-tipped cigarettes (yes vs. no) made little difference for reaching longevity in both sexes (Table 5). We found a significantly inverse association of tar and nicotine exposure with longevity in women, and to lesser extent in men (Table 5).

In Table 6, no risk factors were identified that significantly modified the effect between cigarette smoking status and longevity. In analyses with a longevity cut-off age of 80 years instead of 90 years, the associations between smoking status and longevity became weaker, but remained statistically significant (Table 7).

Table 3: Age- and multivariable-adjusted RRs for reaching longevity according to cigarette smoking frequency, duration, and initiation in birth cohorts of 1916-17; Netherlands Cohort Study (1986-2007).

	Men					Women				
	median	n	90+	Model 1[a] RR (95% CI)	Model 2 [b] RR (95% CI)	median	n	90+	Model 1[a] RR (95% CI)	Model 2[b] RR (95% CI)
Number of cigarettes smoked (N/day) [c]										
Never tobacco	0	305	78	1 (reference)	1 (reference)	0	2,314	844	1 (reference)	1 (reference)
Current smokers										
>0 – 9	6	126	17	0.53 (0.33-0.85)	0.67 (0.36-1.24)	4	86	42	1.03 (0.84-1.25)	0.86 (0.70-1.05)
10- 19	13	274	28	0.40 (0.27-0.60)	0.51 (0.28-0.92)	12	85	22	0.51 (0.36-0.71)	0.48 (0.35-0.68)
20+	20	206	13	0.23 (0.13-0.41)	0.29 (0.14-0.58)	20	100	19	0.47 (0.32-0.69)	0.49 (0.33-0.72)
P for trend[d]				0.014	0.006				<0.001	0.007
Continuous (increment 5 cigt/day)				0.72 (0.64-0.81)	0.77 (0.66-0.90)				0.82 (0.76-0.88)	0.81 (0.75-0.88)
Former smokers										
>0 – 9	5	117	40	0.89 (0.64-1.24)	0.72 (0.50-1.06)	3	337	118	0.96 (0.82-1.12)	0.85 (0.66-1.08)
10- 19	12	316	58	0.72 (0.53-0.98)	0.71 (0.52-0.96)	10	110	36	0.90 (0.68-1.18)	0.86 (0.64-1.14)
20+	20	425	59	0.54 (0.40-0.74)	0.56 (0.40-0.77)	20	83	19	0.63 (0.42-0.93)	0.69 (0.46-1.03)
P for trend[d]				0.007	0.090				0.054	0.325
Continuous (increment 5 cigt/day)				0.92 (0.87-0.98)	0.94 (0.88-1.00)				0.93 (0.88-0.99)	0.94 (0.88-1.00)

Cigarette smoking duration (y)[c]										
Never tobacco	0	305	78	1 (reference)	1 (reference)	0	2,314	844	1 (reference)	1 (reference)
Current smokers										
>0 - <20 yr						12	50	20	1.10 (0.78-1.55)	0.81 (0.55-1.20)
20 - <30	35	29	4	0.53 (0.21-1.34)	0.46 (0.18-1.14)	25	74	19	0.70 (0.48-1.04)	0.52 (0.36-0.76)
30 - <40						35	87	23	0.72 (0.51-1.03)	0.61 (0.43-0.87)
40- <50	46	136	17	0.49 (0.30-0.80)	0.45 (0.26-0.78)	43	143	28	0.54 (0.38-0.75)	0.42 (0.29-0.61)
50+	53	502	41	0.32 (0.22-0.45)	0.33 (0.23-0.48)	51	108	28	0.71 (0.51-0.98)	0.62 (0.44-0.88)
P for trend[d]				0.070	0.454				0.074	0.245
Continuous (5 year increment)				0.90 (0.88-0.93)	0.90 (0.87-0.93)				0.95 (0.93-0.97)	0.93 (0.91-0.95)
Former smokers										
>0 - <20 yr	15	82	23	1.09 (0.74-1.62)	1.13 (0.76-1.68)	10	205	72	0.96 (0.79-1.17)	0.91 (0.72-1.14)
20 - <30	25	181	42	0.91 (0.65-1.26)	0.92 (0.66-1.29)	23	129	36	0.76 (0.58-1.01)	0.71 (0.53-0.96)
30 - <40	34	287	48	0.66 (0.48-0.91)	0.67 (0.48-0.93)	34	105	31	0.81 (0.60-1.09)	0.76 (0.56-1.02)
40- <50	44	282	37	0.51 (0.36-0.74)	0.59 (0.41-0.86)	44	67	25	1.02 (0.75-1.40)	0.94 (0.69-1.28)
50+	51	94	8	0.34 (0.17-0.67)	0.40 (0.20-0.80)					
P for trend[d]				<0.001	<0.001				0.862	0.876
Continuous (5 year increment)				0.93 (0.90-0.95)	0.94 (0.91-0.97)				0.98 (0.95-1.00)	0.97 (0.94-1.00)

Age at cigarette smoking initiation (y) [f]										
Never tobacco	NA	305	78	1 (reference)	1 (reference)	NA	2,314	844	1 (reference)	1 (reference)
Current smokers										
26 or later						36	223	52	0.64 (0.50-0.82)	0.48 (0.36-0.63)
22-25	25	72	8	0.44 (0.22-0.86)	0.40 (0.19-0.83)	25	55	12	0.60 (0.36-0.99)	0.49 (0.30-0.80)
17-21	18	222	23	0.41 (0.26-0.63)	0.40 (0.25-0.65)	18	136	41	0.83 (0.64-1.07)	0.72 (0.55-0.95)
15-16	16	217	20	0.36 (0.23-0.57)	0.45 (0.28-0.73)	15	44	11	0.68 (0.41-1.14)	0.64 (0.38-1.08)
<15	14	153	11	0.28 (0.15-0.51)	0.41 (0.22-0.79)					
P for trend[d]				0.208	0.583				0.274	0.051
Continuous (1 year decrement)				0.99 (0.94-1.04)	1.04 (0.98-1.12)				1.00 (0.98-1.01)	1.01 (0.99-1.02)
Former smokers										
26 or later						34	250	78	0.86 (0.71-1.04)	0.75 (0.58-0.98)
22-25	25	115	24	0.82 (0.55-1.28)	0.77 (0.50-1.18)	24	67	20	0.82 (0.56-1.19)	0.70 (0.46-1.05)
17-21	18	369	66	0.70 (0.52-0.94)	0.71 (0.53-0.97)	18	173	61	0.97 (0.78-1.19)	0.88 (0.67-1.16)
15-16	16	272	47	0.68 (0.49-0.94)	0.77 (0.56-1.06)	16	37	12	0.89 (0.55-1.42)	0.64 (0.36-1.14)
<15	14	188	24	0.50 (0.33-0.76)	0.62 (0.40-0.95)					
P for trend[d]				0.068	0.608				0.461	0.398
Continuous (1 year decrement)				0.97 (0.94-1.00)	0.99 (0.95-1.02)				1.00 (0.99-1.02)	1.01 (0.99-1.02)

a Age adjusted model. b Model adjusted for age (years), body mass index (<18.5, 28.5-25, 25-<30, 30+ kg/m2), non-occupational physical activity (≤30/ >30-60/ >60-90/ >90 min/day), alcohol consumption (0, 0.1-15, >15 g/day), educational level (low, medium, high), and number of diseases at baseline (0,1,2,3 or more). c Model 2 additionally adjusted for smoking duration (continuous; centered). d Never smokers excluded. e Model 2 additionally adjusted for smoking quantity (continuous; centered). f Model 2 additionally adjusted for cigarette-years (continuous; centered).

Table 4: Age- and multivariable-adjusted RRs for reaching longevity according to timing of cigarette smoking cessation in birth cohorts of 1916-17; Netherlands Cohort Study (1986-2007).

	Men					Women				
				Model 1[a]	Model 2 [b]				Model 1[a]	Model 2[b]
	median	n	90+	RR (95% CI)	RR (95% CI)	median	n	90+	RR (95% CI)	RR (95% CI)
Age at cigarette smoking cessation (y)										
Current smokers	NA	679	63	1 (Reference)	1 (Reference)	NA	485	125	1 (Reference)	1 (Reference)
60 or later	65	349	41	1.27 (0.87-1.84)	1.57 (1.09-2.28)	65	225	60	1.03 (0.79-1.35)	1.00 (0.76-1.31)
50-59	55	331	56	1.83 (1.30-2.55)	1.89 (1.33-2.70)	54.5	146	47	1.25 (0.94-1.65)	1.17 (0.88-1.56)
40-49	44	199	43	2.33 (1.63-3.31)	2.05 (1.38-3.04)	44	82	35	1.66 (1.24-2.22)	1.42 (1.02-1.97)
<40	35	74	21	3.05 (1.98-4.69)	2.17 (1.31-3.61)	31	84	32	1.48 (1.08-2.02)	1.27 (0.89-1.81)
Never tobacco	NA	305	78	2.75 (2.03-3.73)	2.55 (1.84-3.54)	NA	2,314	844	1.42 (1.21-1.66)	1.65 (1.38-1.98)
P for trend [c]				<0.001	0.128				0.007	0.011
Time since cigarette smoking cessation (y)										
Current smokers	0	679	63	1 (Reference)	1 (Reference)	0	485	125	1 (Reference)	1 (Reference)
Less than 5 yr	2	179	22	1.33 (0.84-2.09)	1.60 (1.02-2.52)	2	110	33	1.16 (0.84-1.60)	1.15 (0.83-1.60)
5-10	7	163	19	1.25 (0.77-2.04)	1.61 (1.00-2.60)	7	109	27	0.96 (0.67-1.38)	0.89 (0.61-1.31)
10-19	14	336	56	1.80 (1.29-2.52)	1.88 (1.32-2.67)	14	148	46	1.21 (0.91-1.60)	1.14 (0.85-1.52)
20-29	24	201	42	2.25 (1.57-3.21)	1.96 (1.32-2.92)	24	85	36	1.65 (1.23-2.20)	1.40 (1.01-1.93)
30+	34	74	22	3.20 (2.10-4.87)	2.33 (1.42-3.82)	38	85	32	1.46 (1.07-2.00)	1.24 (0.87-1.77)
Never tobacco	NA	305	78	2.75 (2.03-3.73)	2.55 (1.84-3.54)	NA	2,314	844	1.42 (1.21-1.66)	1.66 (1.39-1.99)
P for trend[c]				<0.001	0.101				0.034	0.050
Continuous (5 year increment) [d]				1.16 (1.11-1.22)	1.11 (1.05-1.17)				1.06 (1.03-1.10)	1.04 (1.00-1.08)

a Age adjusted model. b Model adjusted for age (years), body mass index (<18.5, 28.5-25, 25-<30, 30+ kg/m2), non-occupational physical activity (≤30/ >30-60/ >60-90/ >90 min/day), alcohol consumption (0, 0.1-15, >15 g/day), educational level (low, medium, high), number of diseases at baseline (0,1,2,3 or more), and cigarette-years (continuous; centered). c Never- and current smokers excluded.d Never smokers excluded.

Table 5: Age- and multivariable-adjusted RRs for reaching longevity according to inhalation, filter usage, and tar and nicotine exposure to cigarettes in birth cohorts of 1916-17; Netherlands Cohort Study (1986-2007).

	Men					Women				
				Model 1[a]	Model 2[b]				Model 1[a]	Model 2[b]
	median	n	90+	RR (95% CI)	RR (95% CI)	median	n	90+	RR (95% CI)	RR (95% CI)
Cigarette smoke inhalation[c]										
Never tobacco		305	78	1 (reference)	1 (reference)		2,314	844	1 (reference)	1 (reference)
No		389	65	0.65 (0.49-0.88)	0.75 (0.54-1.03)		628	192	0.84 (0.74-0.95)	0.72 (0.57-0.91)
Yes		1,207	156	0.51 (0.40-0.64)	0.67 (0.51-0.88)		369	96	0.71 (0.60-0.85)	0.70 (0.56-0.88)
P-value$_{(yes\ vs.\ no)}$				0.058	0.447				0.131	0.792
Filter-tipped cigarettes usage[c]										
Never tobacco		305	78	1 (reference)	1 (reference)		2,314	844	1 (reference)	1 (reference)
Yes		334	43	0.50 (0.36-0.71)	0.69 (0.48-1.00)		707	219	0.84 (0.75-0.96)	0.74 (0.60-0.92)
No		939	138	0.58 (0.45-0.74)	0.68 (0.52-0.90)		238	59	0.68 (0.54-0.85)	0.61 (0.47-0.80)
P-value$_{(yes\ vs.\ no)}$				0.408	0.915				0.076	0.127
Tar (mg/d)[d]										
Never tobacco	0	305	78	1 (reference)	1 (reference)	0	2,314	844	1 (reference)	1 (reference)
>0 to <200	123	236	38	0.63 (0.45-0.90)	0.75 (0.51-1.10)	54	387	118	0.84 (0.71-0.98)	0.83 (0.64-1.07)
200 to <400	285	337	51	0.59 (0.43-0.81)	0.78 (0.54-1.13)	270	107	19	0.49 (0.32-0.73)	0.58 (0.36-0.92)
≥400	540	272	31	0.45 (0.30-0.65)	0.63 (0.42-0.95)	468	32	4	0.34 (0.13-0.85)	0.43 (0.17-1.04)
P for trend[††]				<0.001	0.039				<0.001	0.004
Continuous (increment of 100 mg/d)				0.87 (0.81-0.94)	0.92 (0.85-1.00)				0.77 (0.69-0.85)	0.82 (0.73-0.93)
Nicotine (mg/d) [d]										
Never tobacco	0	305	78	1 (reference)	1 (reference)	0	2,314	844	1 (reference)	1 (reference)
>0 to <10	6.2	126	29	0.90 (0.62-1.31)	0.98 (0.65-1.48)	3.5	317	103	0.89 (0.75-1.05)	0.87 (0.66-1.14)
10 to <20	14.9	200	28	0.55 (0.37-0.82)	0.70 (0.46-1.07)	14.0	103	23	0.61 (0.43-0.88)	0.70 (0.48-1.03)

20 to <30	24.0	191	22	0.45 (0.29-0.70)	0.61 (0.38-0.99)	22.5	75	13	0.47 (0.29-0.78)	0.58 (0.35-0.99)
≥30	42.0	335	42	0.49 (0.35-0.69)	0.67 (0.46-0.99)	35.0	34	3	0.24 (0.8-0.71)	0.29 (0.10-0.85)
P for trend[e]				<0.001	0.013				<0.001	0.001
Continuous (increment of 10 mg/d)				0.88 (0.79-0.99)	0.94 (0.85-1.04)				0.71 (0.62-0.82)	0.78 (0.67-0.91)

a Age-adjusted model. b Model adjusted for age (years), body mass index (<18.5, 28.5-25, 25-<30, 30+ kg/m2), non-occupational physical activity (≤30/ >30-60/ >60-90/ >90 min/day), alcohol consumption (0, 0.1-15, >15 g/day), educational level (low, medium, high), and number of diseases at baseline (0,1,2,3 or more). c Model additionally adjusted for cigarette smoking quantity (continuous; centered) ,cigarette smoking duration (continuous; centered) and current smoker (yes/no). d Model additionally adjusted for cigarette smoking duration (continuous; centered) and current smoker (yes/no). e Never smokers excluded.

Table 6: Multivariable-adjusted[a] Risk Ratios for reaching longevity according to exclusively cigarette smoking status, by strata of potentially important lifestyle factors in birth cohorts of 1916-17; Netherlands Cohort Study (1986-2007).

	Men				Women			
	Never smokers	Former smokers	Current smokers	*P*-trend	Never smokers	Former smokers	Current smokers	*P*-trend
Overall								
Survivors (90+)/ n	78/305	156/900	58/616		844/2,314	161/497	114/442	
RR (95%CI)	1 (reference)	0.68 (0.53-0.94)	0.47 (0.33-0.66)	<0.001	1 (reference)	0.70 (0.57-0.86)	0.61 (0.52-0.78)	<0.001
P-interaction (gender)							0.040	
Body Mass Index (BMI)								
18.5- <25 kg/m^2								
Survivors (90+)/ n	47/162	86/455	31/356		459/1,172	92/262	77/265	
RR (95%CI)	1 (reference)	0.72 (0.52-1.01)	0.35 (0.22-0.56)	<0.001	1 (reference)	0.70 (0.52-0.93)	0.62 (0.50-0.77)	<0.001
≥25 kg/m^2								
Survivors (90+)/ n	31/139	70/442	25/249		378/1,115	69/232	37/169	
RR (95%CI)	1 (reference)	0.67 (0.45-1.00)	0.62 (0.37-1.02)	0.048	1 (reference)	0.67 (0.50-0.90)	0.60 (0.44-0.82)	<0.001
P-interaction			0.663				0.883	
Non-occupational physical activity								
≤30 min/day								
Survivors (90+)/ n	10/72	35/218	9/153		273/810	43/162	40/164	
RR (95%CI)	1 (reference)	1.15 (0.58-2.30)	0.67 (0.28-1.61)	0.401	1 (reference)	0.58 (0.40-0.85)	0.63 (0.47-0.85)	0.001
>30-60 min/day								
Survivors (90+)/ n	26/88	47/257	16/201		276/708	58/153	37/117	
RR (95%CI)	1 (reference)	0.54 (0.34-0.86)	0.43 (0.22-0.82)	0.004	1 (reference)	0.84 (0.61-1.17)	0.71 (0.54-0.95)	0.017
>60-90 min/day								
Survivors (90+)/ n	19/58	28/177	12/106		167/433	29/98	23/79	
RR (95%CI)	1 (reference)	0.56 (0.32-0.97)	0.34 (0.16-0.74)	0.003	1 (reference)	0.64 (0.40-1.03)	0.63 (0.43-0.95)	0.016

>90 min/day								
Survivors (90+)/ n	23/87	46/248	21/156		128/363	31/84	14/82	
RR (95%CI)	1 (reference)	0.72 (0.45-1.15)	0.49 (0.27-0.87)	0.013	1 (reference)	0.69 (0.39-1.21)	0.45 (0.26-0.77)	0.003
P-interaction			0.178				0.506	
Alcohol consumption								
0 g/day								
Survivors (90+)/ n	23/108	18/138	11/107		307/966	27/112	17/114	
RR (95% CI)	1 (reference)	0.56 (0.30-1.03)	0.71 (0.34-1.47)	0.134	1 (reference)	0.56 (0.32-0.98)	0.49 (0.29-0.69)	<0.001
0.1-15 g/day								
Survivors (90+)/ n	44/160	85/458	26/298		487/1,224	106/290	60/213	
RR (95% CI)	1 (reference)	0.79 (0.57-1.10)	0.39 (0.24-0.65)	<0.001	1 (reference)	0.74 (0.56-0.98)	0.62 (0.49-0.79)	<0.001
>15 g/day								
Survivors (90+)/ n	11/37	53/304	21/211		50/124	28/95	37/115	
RR (95% CI)	1 (reference)	0.56 (0.31-1.03)	0.46 (0.23-0.89)	0.038	1 (reference)	0.70 (0.46-1.05)	0.76 (0.53-1.09)	0.118
P-interaction			0.241				0.426	
Educational level								
Primary/ Lower vocational education								
Survivors (90+)/ n	36/148	74/439	32/350		506/1,486	66/211	44/220	
RR (95% CI)	1 (reference)	0.64 (0.44-0.95)	0.40 (0.25-0.64)	<0.001	1 (reference)	0.82 (0.61-1.12)	0.56 (0.43-0.73)	<0.001
Junior/senior high school								
Survivors (90+)/ n	21/91	53/350	16/192		273/668	80/232	54/182	
RR (95% CI)	1 (reference)	0.66 (0.42-1.04)	0.43 (0.22-0.85)	0.009	1 (reference)	0.65 (0.49-0.86)	0.61 (0.48-0.79)	<0.001
Higher vocational/ University education								
Survivors (90+)/ n	21/66	29/111	10/74		65/160	15/54	16/40	
RR (95% CI)	1 (reference)	0.82 (0.47-1.44)	0.56 (0.28-1.15)	0.107	1 (reference)	0.42 (0.21-0.85)	0.71 (0.40-1.25)	0.253

P-interaction			0.909				0.348	
History of (selected) diseases[b]								
No history of disease								
Survivors (90+)/ n	65/214	118/516	48/423		701/1,680	125/334	99/336	
RR (95% CI)	1 (reference)	0.73 (0.55-0.97)	0.42 (0.29-0.61)	<0.001	1 (reference)	0.73 (0.58-0.91)	0.63 (0.53-0.76)	<0.001
History of disease								
Survivors (90+)/ n	69/240	126/632	49/468		724/1,819	135/375	101/354	
RR (95% CI)	1 (reference)	0.65 (0.49-0.85)	0.43 (0.30-0.63)	<0.001	1 (reference)	0.71 (0.57-0.88)	0.63 (0.53-0.76)	<0.001
P-interaction			0.989				0.840	

a Model adjusted for age (years), smoking quantity (continuous, centered), smoking duration (continuous, centered), body mass index (<18.5, 28.5-25, 25-<30, 30+ kg/m2), non-occupational physical activity (≤30/ >30-60/ >60-90/ >90 min/day), alcohol consumption (0, 0.1-15, >15 g/day), educational level (low, medium, high), and number of diseases at baseline (0,1,2,3 or more). b Diseases included, any type of cancer, asthma, chronic bronchitis, angina pectoris, heart attack, stroke and diabetes.

Table 7: Age- and multivariable-adjusted RRs for reaching 80 years of age according to overall and tobacco specific smoking status in birth cohorts of 1916-17; Netherlands Cohort Study (1986-2007).

	Men				Women			
			Model 1[a]	Model 2[b]			Model 1[a]	Model 2[b]
	n	80+	RR (95% CI)	RR (95% CI)	n	80+	RR (95% CI)	RR (95% CI)
Tobacco smoking status								
Overall tobacco								
Never	305	226	1 (reference)	1 (reference)	2,314	1,909	1 (reference)	1 (reference)
Former	1,605	1,014	0.85 (0.79-0.92)	0.88 (0.81-0.95)	550	442	0.97 (0.93-1.02)	0.96 (0.92-1.01)
Current	1,373	757	0.74 (0.69-0.81)	0.75 (0.69-0.81)	495	373	0.91 (0.87-0.96)	0.90 (0.85-0.95)
P for trend			<0.001	<0.001			0.001	<0.001
P-interaction$_{(sex)}$[b]								<0.001
Exclusively cigarettes[c]								
Former	955	601	0.85 (0.78-0.92)	0.87 (0.80-0.94)	548	440	0.97 (0.93-1.02)	0.96 (0.92-1.01)
Current	679	344	0.68 (0.62-0.76)	0.68 (0.62-0.75)	485	366	0.91 (0.87-0.97)	0.90 (0.85-0.95)
P for trend			<0.001	<0.001			0.001	<0.001
P-interaction$_{(sex)}$[b]								<0.001
Exclusively cigarettes (adjusted for smoking quantity and duration)[c]								
Former	900	570	0.86 (0.79-0.94)	0.86 (0.79-0.94)	497	398	0.94 (0.88-1.00)	0.93 (0.87-0.99)
Current	616	312	0.77 (0.68-0.86)	0.73 (0.65-0.82)	442	338	0.92 (0.87-0.97)	0.90 (0.85-0.95)
P for trend			<0.001	<0.001			0.001	<0.001
P-interaction$_{(sex)}$[b]								<0.001
Exclusively cigars[c]								
Former	42	28	0.89 (0.71-1.11)	0.95 (0.77-1.18)	1	1	NA	NA
Current	76	63	1.11 (0.98-1.25)	1.09 (0.97-1.23)	3	3	NA	NA
P for trend			0.208	0.224				

Exclusively pipe[c]								
Former	7	5	0.98 (0.60-1.60)	1.06 (0.68-1.66)	0	0	NA	NA
Current	27	12	0.60 (0.39-0.92)	0.58 (0.39-0.88)	0	0	NA	NA
P for trend			0.019	0.011				
Exclusively cigar and/or pipe[c]								
Former	68	44	0.86 (0.71-1.04)	0.91 (0.76-1.08)	1	1	NA	NA
Current	141	98	0.93 (0.82-1.06)	0.92 (0.81-1.05)	3	3	NA	NA
P for trend			0.194	0.189				
Exclusively cigarettes with cigar and/or pipe[§]								
Former[¶]	582	369	0.85 (0.78-0.93)	0.89 (0.81-0.97)	1	1	NA	NA
Former cigarette, current cigar and/or pipe	160	89	0.75 (0.64-0.87)	0.78 (0.67-0.91)	1	1	NA	NA
Current cigarette, former cigar and/or pipe	35	18	0.69 (0.50-0.96)	0.75 (0.55-1.03)	0	0	NA	NA
Current[††]	357	208	0.78 (0.70-0.87)	0.80 (0.71-0.89)	6	3	NA	NA

a Age adjusted model.b Model adjusted for age (years), body mass index (<18.5, 28.5-25, 25-<30, 30+ kg/m2), non-occupational physical activity (≤30/ >30-60/ >60-90/ >90 min/day), alcohol consumption (0, 0.1-15, >15 g/day), educational level (low, medium, high), and number of diseases at baseline (0,1,2,3 or more).c Using never tobacco smokers as a reference.

Discussion

In this large prospective cohort study of those born in 1916 and 1917, tobacco smoking was significantly inversely associated with the chance of reaching longevity, defined as 90 years of age, in both sexes. The use of specific tobacco products (cigarette, cigars, and pipe) showed comparable results. The association between smoking status and longevity was stronger in men than in women. Several cigarette smoking habits were independently associated with reaching longevity, including cigarette smoking quantity, duration, cessation and exposure to tar and nicotine. Among former smokers, age at smoking cessation was inversely associated with reaching longevity. In men, quitting smoking after the age of 60 years was still found to increase the chance of reaching longevity compared to current smokers at the age of 68-70 years. No significant associations were found with age at smoking initiation.

Unlike previous studies (9, 11, 18), the NLCS is the first cohort study in which a significant association between smoking status and longevity has been found in women. Even though smoking affected reaching longevity in both sexes, the association was somewhat stronger in men than in women. There are several mortality studies in which the association between smoking habits, and short- and long term mortality has been assessed. In a meta-analysis on smoking and mortality in older adults it was also concluded that the effect estimate of smoking status on mortality was somewhat stronger in men than in women (19).

A possible explanation for the differences between men and women regarding smoking status and longevity may be the result of underlying differences in smoking habits. In our study, women had smoked on average smaller amounts of cigarettes, and a shorter period of time. After additional adjustment for smoking quantity and duration, the effect estimates on smoking status and longevity became more comparable between men and women. However, gender still acted as a significant effect-modifier between smoking status and longevity after this adjustment. Another possible explanation could be that never smoking women are more often exposed to passive smoking than never smoking men, which might have led to an underestimation of the association between active smoking and longevity in women. Given the small number of women who have never been exposed to active or passive smoking in the NLCS, we were unable to check whether this was the case. Few studies have examined other aspects of smoking besides smoking status on reaching longevity, and those who did only focused on smoking quantity (1, 2). In these studies, increasing cigarette smoking quantity was significantly inversely associated with reaching the age of 75 years in both sexes (1), and reaching 85 years in men (2). Similarly, several mortality studies in older adults observed dose response relationships of increasing mortality with increasing number of cigarettes (20-22), and smoking duration (21, 23).

Similarly to smoking status, the association of smoking quantity and duration with longevity seemed stronger in men than in women. In contrast, we observed that the inverse association of exposure to tar and nicotine with longevity seemed stronger

in women than in men. In another study, the association of increasing exposure to cigarette components, including tar and nicotine, with mortality from respiratory and cardiovascular disease was found to be stronger in women than in men (24). Furthermore, there is some evidence that women who smoke are relatively deficient in estrogen (25). This indicates that women might be more susceptible to tar and nicotine than men. In our study, we observed that female smokers smoked on average more often a light type of tobacco, and filter-tipped cigarettes than men. As a result, the average cumulative exposure to tar and nicotine per cigarette might be lower in female smokers than in male smokers. This might explain why we did observe a somewhat stronger effect of cigarette smoking quantity in men compared to women, despite a potentially higher susceptibility to tar and nicotine in women. However, this explanation is speculative, and should be further explored in future studies.

Quitting smoking after the age of 60 was significantly associated with an increased chance of reaching longevity compared to current smokers. One other study has assessed the relation of quitting smoking after the age of 50 with reaching the age of 90 years and reported no significant association, but data were not shown (8). Similar to our study, mortality studies in older adults found a decreasing risk on mortality with earlier ages at smoking cessation, and increasing time since smoking cessation in both sexes (20, 22).

To our knowledge, this is the first study that has assessed the relationship of cigar and pipe usage, with reaching longevity. Our findings suggest that, in addition to cigarette smoking, pipe and cigar smoking are both associated with a decreased chance of reaching longevity.

Results of our additional sensitivity analyses using a longevity cut-off age of 80 instead of 90 years were in line with the results of a previous study, which also studied the relationship between smoking status and longevity using different cut-off ages (5). These findings, together, illustrate that the strength of the association between smoking status and reaching longevity may vary using different cut-off ages.

An important strength of this study is the prospective character and completeness of follow-up. Furthermore, we had extensive data on various smoking habits, making it possible to investigate as well as adjust for several smoking characteristics. Nonetheless, some caution is needed when interpreting these results. When investigating smoking habits that are highly correlated with each other, the problem of multi-collinearity may arise (26). We tried to reduce collinearity between smoking factors by centering and combining smoking variables, but there might still be some risk that multi-collinearity has influenced our results (26).

One limitation of this study is that no information was collected on changing smoking habits after baseline measurement. Although few people will start smoking at an older age, some cohort members might have quit smoking during follow-up,

and would still be classified as a current smoker in our analyses (27). This might have led to an underestimation of the association between smoking and longevity. Furthermore, the participants were aged 68-70 years at baseline. This means that these participants already survived to an advanced age. Therefore, the effect of smoking on reaching longevity might be stronger in younger cohorts.

In conclusion, the inverse association between smoking and longevity was stronger in men, than in women. The deleterious effect of cigarette smoking on longevity seemed to strengthen with increasing smoking quantity and duration, which may partially explain the observed difference between sexes. Overall, never smokers of both sexes had the highest chance of reaching longevity. Quitting smoking significantly increased the chance of reaching longevity compared to current smokers at the age of 68-70 years, in men even quitting beyond the age of 60 years.

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Chapter 5

Body size, non-occupational physical activity and the chance of reaching longevity in men and women: Findings from the Netherlands Cohort Study

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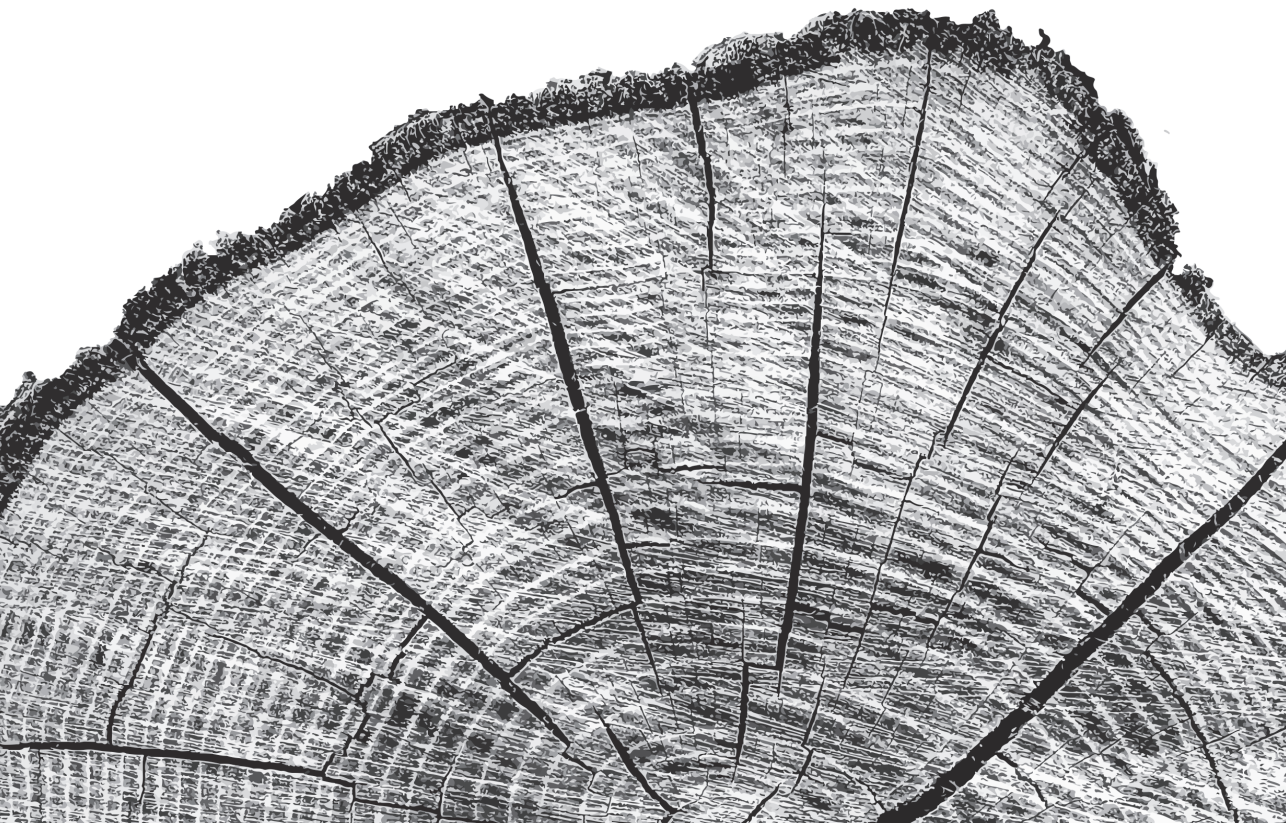

Body size, non-occupational physical activity and the chance of reaching longevity in men and women: Findings from the Netherlands Cohort Study

Lloyd Brandts, Piet A. van den Brandt

Abstract

Introduction
The rising number of obese- and/or physically inactive individuals might negatively impact human lifespan. This study assessed the association between height, Body Mass Index (BMI) and non-occupational physical activity, and the likelihood of reaching 90 years of age, in both sexes separately.
Methods
Analyses were conducted using data from the Netherlands Cohort Study (NLCS). Participants born in 1916-17 (n=7,807) completed a questionnaire in 1986 (at age 68-70), and were followed up for vital status information until the age of 90 years (2006-07). Cox regression analyses were based on 5,479 participants with complete data, to calculate Risk Ratios (RR) of reaching longevity (age 90 years).
Results
In women, we observed significant associations between reaching longevity and height (RR, 1.05; 95% confidence interval (CI), 1.00-1.09 per 5 cm increment), BMI at baseline (≥30 vs. 18.5-<25 kg/m2; RR, 0.68; 95% CI, 0.54-0.86), and BMI change since age 20 years (≥8 vs. 0-<4 kg/m2; RR, 0.81; 95% CI, 0.66-0.98). In men, height and BMI were not associated with reaching longevity. In women, non-occupational physical activity showed an inverse U-shaped association with reaching longevity, with the highest RR around 60 minutes of physical activity per day. In men, a positive linear association was observed between physical activity and reaching longevity.
Conclusion
This study indicates that body size and physical activity are related to the likelihood of reaching 90 years of age, and that these associations differ by sex.

Introduction

With an increasing life expectancy in recent decades, the absolute number of elderly reaching longevity (>90 years of age) is expected to quadruple by 2060(1). However, recent data from the United States and United Kingdom suggest that the increase in life-expectancy is leveling-off (2, 3). One commonly used argument for the potential stagnating life expectancy is the growing number of obese and/or physically inactive individuals worldwide (4, 5). However, studies that prospectively studied the association between these factors and reaching old age, or longevity, are limited.

Regarding body mass, six studies have been performed assessing the relationship between BMI and longevity (6-11). Across these studies, a decreased chance of reaching longevity could be observed in both extremes (i.e. high and low) of the BMI spectrum. Regarding physical activity, seven studies have assessed the association with reaching longevity (6, 8, 9, 12-15). In these studies, physical activity was positively associated with the chance of reaching longevity.

Most of the current longevity studies investigated men only (6-9, 13), or combined both sexes(10, 14, 16). However, men and women follow different survival patterns, which may be determined by differences in hormones, genetics, and/or lifestyle (17, 18). Therefore, it would be interesting to investigate the relation between BMI and physical activity, and longevity separately for men and women.

Using the prospective Netherlands Cohort Study (NLCS), the aim here was to quantify the association between height, several dimensions of BMI and non-occupational physical activity, and the chance of reaching longevity, defined as reaching the age of 90 years in men and women separately.

Methods

Study design and population

The NLCS was initiated in 1986 as a large prospective cohort study, and included 120,852 men and women aged 55 to 69 years from 204 Dutch municipalities (19). Baseline information was collected in 1986 on cancer risk factors using a self-administrated questionnaire. The full NLCS 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. Because only a small part of the cohort was “at risk” of reaching the age of 90 years in 2007, the data entry was restricted to the oldest birth cohort (1916, and 1917) of the NLCS cohort (i.e. aged 68-70 years at baseline).

Vital status information of the longevity cohort until the age of 90 years was >99.9% complete. The study population consisted of 3,646 men and 4,161 women (Figure 1). The NLCS study has been approved by the institutional review boards of Maastricht University and the Netherlands Organisation for Applied Scientific Research TNO (Zeist).

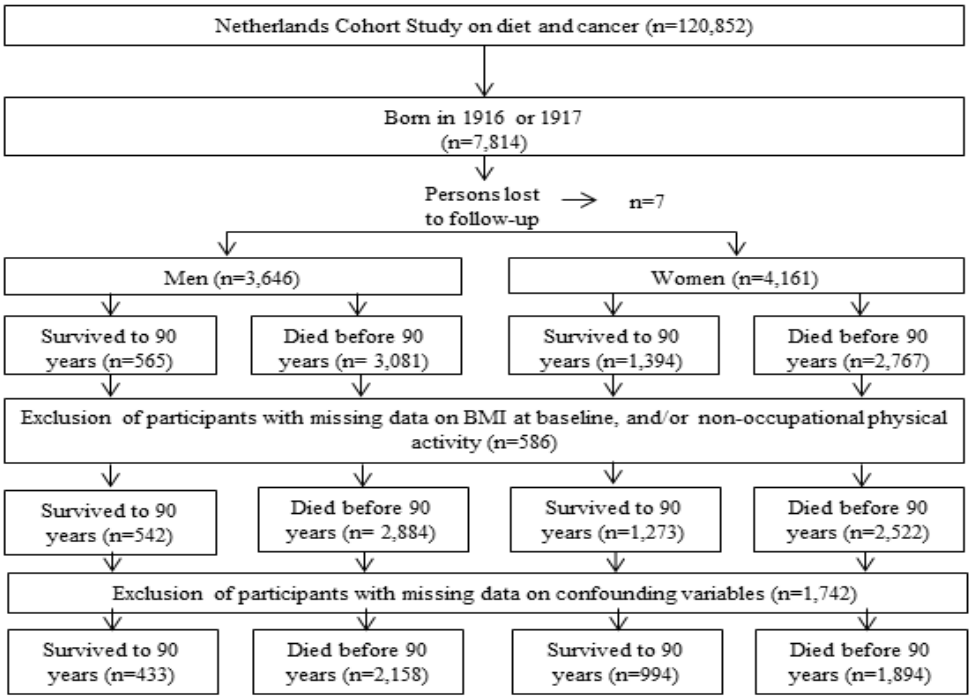

Figure 1: Flow diagram on analyses of height, BMI, and non-occupational physical activity with longevity.

Exposure assessment

At baseline, participants completed a self-administered questionnaire, including detailed information on weight, height, weight at age 20 years and non-occupational physical activity. BMI categories at baseline were based on the WHO International Classification (<18.5 kg/m2/18.5-<25 kg/m2/≥25-<30 kg/m2/ ≥30 kg/m2)(20). For the analyses on BMI at age 20,other categories were used, namely <20, 20-<21.5, 21.5-<23, 23 to <25, and ≥25kg/m2. BMI at baseline minus BMI at age 20 years was used to calculate change in BMI since the age of 20 years, and was categorized as <0, 0 to <4, 4 to <8, and ≥8 kg/m2. These categorizations have been used before in other NLCS analyses (21, 22). For these analyses, we assumed that height at age 20 years was similar to the height of the participant at baseline.

At baseline, participants were asked "How many minutes do you spend on average per day walking/cycling to your work, to go shopping, or to walk the dog?" and "How many hours of leisure time do you spend on average per week on 1) recreational walking/cycling, 2)gardening/doing odd jobs, and 3)sports/gymnastics?". The reported times from both questions were summed to calculate an overall measure of total non-occupational physical activity with categories of ≤30,>30-60,>60-90, and >90min/day.

S*tatistical analyses*
Baseline characteristics were presented by sex and survival status at age 90 years. The characteristics were presented in percentages and with mean values including SD for categorical and continuous variables, respectively.
The associations of body size, and non-occupational physical activity with the chance of reaching longevity were evaluated using Cox regression models with a fixed follow-up time(23, 24). Standard errors were calculated using the Huber-White sandwich estimator to account for underdispersion(25). A priori factors were selected as potential confounders based on the literature, and included age at baseline, smoking status, cigarettes smoked per day, cigarette smoking duration in years, alcohol consumption, educational level, energy intake, and depending on the analyses additionally adjusted for sex, baseline weight, BMI at age 20 years, BMI at baseline, and non-occupational physical activity. Other co-variables considered included marital status, vegetables intake, fruit intake, fish intake, red meat intake, and total meat intake. None of these changed the effect estimates more than 10%, and were therefore not included in the analyses.

In trend analyses, ordinal variables were fitted as continuous variables. Restricted cubic spline regression analyses using three knots at the 10th, 50th, and 90th percentile, and Wald test were performed to test for non-linearity.
Wald tests for interaction and cross-product terms were used to evaluate potential effect-modification by sex, smoking- and disease status. Selected diseases at baseline included heart attack, angina pectoris, stroke, any type of cancer, asthma, bronchitis and diabetes. Regarding BMI and longevity, additional analyses have been performed to test for linearity in never smokers, non-diseased individuals and non-diseased never smokers. All analyses were performed using Stata 15.0 (StataCorp. 2017. College Station, TX).

Results
Among men included in our analyses, 433 (16.7%) survived to the age of 90 years (Table 1). Male survivors and non-survivors were comparable regarding average height, BMI at baseline, BMI at age 20 years and change in BMI since the age of 20 years, but survivors spent more time on non-occupational physical activity per day. Among women included in our analyses, 994 (34.4%) survived to 90 years of age (Table 1). Compared to female non-survivors, female survivors were on average taller, had a somewhat lower average BMI at baseline, and had a lower average increase in BMI since the age of 20 years. Furthermore, female survivors had more often a higher level of physical activity than female non-survivors (Table 1).

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

	Men		Women	
	Survivors	Non-survivors	Survivors	Non-survivors
N[a]	433	2,158	994	1,894
Height (cm), mean (SD)	175.1 (6.7)	175.0 (6.7)	164.4 (6.2)	163.9 (6.5)
Height (cm), %				
<160	2.1	1.0	21.6	25.4
160-<165	3.5	5.0	29.9	28.3
165-<170	16.8	16.7	34.4	33.3
170-<175	23.7	21.5	8.4	8.6
175-<180	32.0	34.1	5.1	4.1
180-<185	13.6	12.6	0.5	0.2
185+	8.3	9.1	0.1	0.1
BMI (kg/m^2) at baseline, mean (SD)	24.7 (2.5)	24.9 (2.7)	24.8 (3.1)	25.2 (3.7)
BMI (kg/m^2) at baseline, %				
<18.5	0.7	1.1	0.9	1.7
18.5 to <25	58.7	53.3	56.4	50.6
25 to <30	37.2	42.0	36.6	37.3
30+	3.4	3.6	6.1	10.4
BMI (kg/m^2) at age 20 years, mean (SD)[b]	21.8 (2.6)	21.9 (2.4)	21.4 (2.7)	21.4 (2.8)
BMI (kg/m^2) at age 20 years, %[b]				
<20	20.6	19.0	29.5	31.8
20 to <21.5	24.5	26.1	25.9	25.2
21.5 to <23	26.5	25.0	21.8	19.9
23 to <25	20.1	21.3	15.8	15.3
25+	8.3	8.6	7.0	7.8
Change in BMI (kg/m^2) since age 20 years, mean (SD)[b]	2.9 (3.2)	2.9 (3.1)	3.5 (3.7)	3.9 (4.0)
Change in BMI (kg/m^2) since age 20 years, %[b]				
<0	13.3	15.1	14.6	13.2
0 to <4	57.8	50.6	42.8	40.0
4 to <8	22.7	29.2	33.0	33.5
8+	6.2	5.1	9.6	13.3
Non-occupational physical activity (min/day), mean (SD)	81.8 (71.5)	72.6 (61.3)	55.8 (47.5)	55.5 (49.6)
Non-occupational physical activity, %				
≤30 min/day	17.1	23.2	31.7	35.5
>30-60 min/day	31.5	30.4	33.3	28.8

>60-90 min/day	20.1	18.6	19.5	18.7
>90 min/day	31.3	27.8	15.5	17.0
Year of birth, %				
1916	22.9	22.9	23.3	23.1
1917	77.1	77.1	76.7	76.9

[a] Number of participants with complete information on height, BMI at baseline, non-occupational physical activity, and confounders including: year of birth, tobacco smoking status, cigarette smoking quantity, cigarette smoking duration, educational level, alcohol consumption and energy intake. [b] Number of participants used may vary from the study population due to missing values on specific exposure variables.

In multivariable-adjusted analyses, no significant associations were found between reaching longevity and height, BMI at baseline, BMI at age 20 years and change in BMI since age 20 in men (Table 2). In women, a significant association was observed between reaching longevity and height, BMI at baseline and increase in BMI since the age of 20 years. Women taller than 175 cm had an increased chance (RR, 1.31; 95%CI, 1.01-1.68) of reaching longevity compared to women shorter than 160 cm. Obese women (≥30 kg/m2) had a RR of 0.68; 95%CI, 0.54-0.86 of reaching longevity compared to normal weight women. In underweight women, a non-statistically significantly inverse association (RR, 0.61; 95%CI, 0.35-1.09) was observed with reaching longevity compared to normal weight women. Women who gained 8kg/m2 or more since the age of 20 years had a significantly reduced chance (RR, 0.81; 95%CI, 0.66-0.98) of reaching longevity compared to women who gained 0-<4 kg/m2. As in men, no significant associations were found between BMI at age 20 years and reaching longevity in women (Table 2).

In table 2, men who reported >90 min of non-occupational physical activity per day were more likely to reach longevity compared to those who reported ≤30 min/day (RR, 1.39; 95%CI, 1.07-1.82). The association between non-occupational physical activity seemed to strengthen with increasing categories of physical activity (RR, 1.05 per increment of 30 min/day; 95%CI, 1.02-1.09). In women, a significantly increased chance of reaching longevity was found for those who reported >30-60 min/day of non-occupational physical activity (RR, 1.21;95%CI, 1.07-1.37) compared to those with 30min/day of non-occupational physical activity or less. The effect estimate became weaker and non-significant in higher categories of non-occupational physical activity.

Restricted cubic spline analyses (Figure 2) showed a non-linear association between BMI at baseline (P<0.001) with reaching longevity in women, but not in men. In women, a non-linear association was also observed between non-occupational physical activity and reaching longevity (P=0.003), with the highest RR around 60 minutes of non-occupational physical activity per day.

Table 2: Age- and multivariable-adjusted RRs for reaching longevity according to height, BMI at baseline, BMI at age 20, Change in BMI since age 20 years, and non-occupational physical activity in birth cohorts of 1916-17; Netherlands Cohort Study (1986-2007).

	Men							Women						
				Model 1[a]		Model 2[b]					Model 1[a]		Model 2[b]	
	median	n	90+	RR	95% CI	RR	95% CI	median	n	90+	RR	95% CI	RR (95% CI)	
Height (cm)[c]														
<160								156	646	199	reference		reference	
160-<165	167	507	84	reference		reference		162	774	276	1.16	1.00-1.34	1.15	0.99-1.33
165-<170								167	905	317	1.14	0.98-1.32	1.15	1.00-1.34
170-<175	172	675	112	1.00	0.78-1.30	0.99	0.76-1.28	171	422	148	1.14	0.96-1.36	1.12	0.93-1.34
175-<180	176	755	120	0.96	0.75-1.24	0.93	0.71-1.21							
180-<185	182	453	86	1.15	0.87-1.51	1.03	0.77-1.39	176	141	54	1.24	0.98-1.58	1.31	1.01-1.68
185+	187	201	31	0.94	0.64-1.37	0.87	0.56-1.34							
P for trend				0.732		0.726					0.074		0.070	
Continuous (increment 5cm)				1.02	0.95-1.08	0.99	0.92-1.07				1.04	1.00-1.08	1.05	1.00-1.09
P-interaction[d]													0.026	
BMI at baseline (kg/m^2)[e]														
<18.5	17.5	26	3	0.63	0.22-1.85	0.77	0.26-2.24	17.7	40	9	0.61	0.34-1.09	0.61	0.35-1.09
18.5-<25	23.5	1,404	254	reference		reference		23.0	1,519	560	reference		reference	
25-<30	26.4	1,068	161	0.83	0.69-1.00	0.88	0.73-1.06	26.6	1,071	364	0.92	0.83-1.03	0.93	0.84-1.04
30+	31.1	93	15	0.89	0.55-1.44	1.00	0.63-1.60	31.6	258	61	0.64	0.51-0.81	0.68	0.54-0.86
P for trend[f]				0.077		0.287					<0.001		0.002	
Continuous[f] (increment 1 kg/m^2)				0.97	0.94-1.01	0.98	0.95-1.02				0.98	0.96-0.99	0.98	0.97-1.00
P-interaction[d]													0.418	

BMI at age 20 (kg/m^2)[e]														
<20	19.1	389	70	1.13	0.85-1.51	1.08	0.81-1.44	18.8	792	264	0.93	0.81-1.08	0.94	0.82-1.08
20-<21.5	20.8	521	83	reference		reference		20.8	651	232	reference		reference	
21.5-<23	22.2	511	90	1.11	0.85-1.46	1.10	0.84-1.43	22.1	526	195	1.04	0.90-1.21	1.04	0.89-1.21
23-<25	23.7	426	68	1.00	0.75-1.35	1.00	0.75-1.33	23.9	396	141	1.00	0.84-1.18	1.00	0.85-1.19
25+	26.0	173	28	1.01	0.69-1.50	1.03	0.70-1.53	26.3	192	63	0.92	0.73-1.15	0.97	0.77-1.21
P for trend				0.614		0.811					0.591		0.412	
Continuous (increment 1 kg/m^2)				0.98	0.94-1.03	0.99	0.95-1.03				1.00	0.98-1.02	1.01	0.99-1.02
P-interaction[d]													0.871	
Change in BMI since age 20 (kg/m^2)[g]														
<0	-1.4	299	45	0.80	0.60-1.08	0.90	0.67-1.21	-1.6	351	131	1.02	0.87-1.19	1.07	0.91-1.27
0-<4	2.3	1,046	196	reference		reference		2.3	1,048	383	reference		reference	
4-<8	5.2	568	77	0.72	0.57-0.92	0.74	0.57-0.94	5.5	852	295	0.95	0.84-1.07	0.97	0.86-1.09
8+	9.3	107	21	1.05	0.70-1.58	1.01	0.67-1.52	9.5	306	86	0.77	0.63-0.94	0.81	0.66-0.98
P for trend				0.576		0.291					0.011		0.024	
Continuous (increment 1kg/m^2)				0.99	0.96-1.03	0.99	0.95-1.02				0.98	0.97-1.00	0.98	0.96-1.00
P-interaction[d]													0.055	
Non-occupational physical activity (min/day)[h]														
≤30	21.4	569	69	reference		reference		17.1	972	299	reference		reference	
>30-60	42.9	794	137	1.42	1.09-1.86	1.34	1.02-1.75	42.9	898	353	1.27	1.13-1.45	1.21	1.07-1.37
>60-90	72.9	489	88	1.49	1.11-1.99	1.28	0.96-1.71	72.9	542	187	1.12	0.97-1.30	1.05	0.90-1.22
>90	132.9	739	139	1.55	1.19-2.03	1.39	1.07-1.82	115.7	476	155	1.06	0.90-1.24	1.00	0.85-1.17

P for trend	0.002		0.036			0.494		0.814		
Continuous (increment 30 min/ day)	1.06	1.03-1.09	1.05	1.02-1.09		1.00	0.97-1.03	0.99	0.96-1.02	
P-interaction[d]								0.100		

[a] Age adjusted model. [b] Model adjusted 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 (low, medium, high), and energy intake (kcal, continuous). [c] Additionally adjusted for weight in kg (continuous). [d] Wald test for interaction between main exposure and sex.[e] Additionally adjusted for non-occupational activity (≤30/ >30-60/ >60-90/ >90 min/day). [f] Participants with BMI <18.5 kg/m2 excluded. [g] Additionally adjusted for non-occupational activity (≤30/ >30-60/ >60-90/ >90 min/day) and BMI at age 20 years (in kg/m2, continuous). [h] Additionally adjusted for BMI at baseline (<18.5, 28.5-25, 25-<30, 30+ kg/m2).

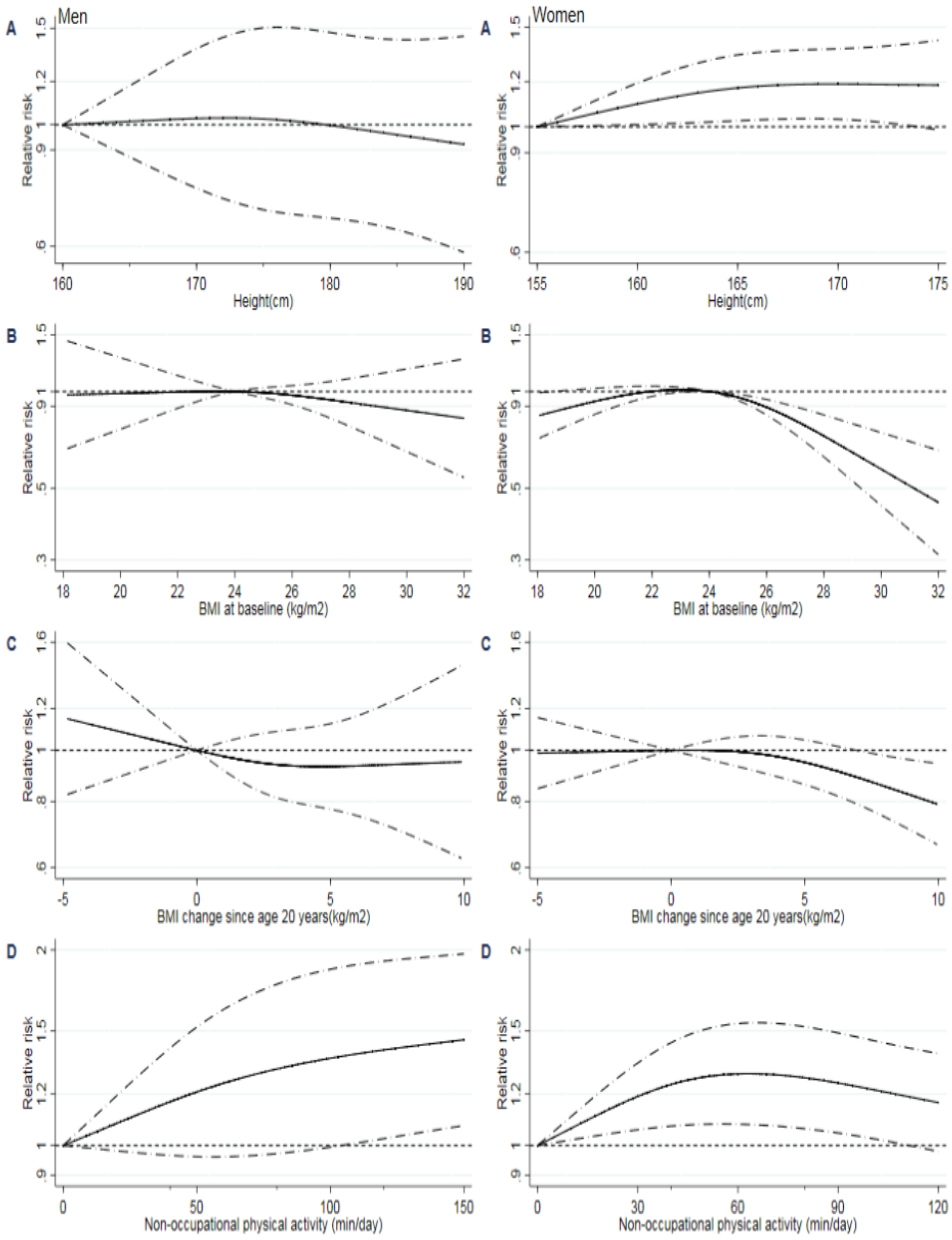

Figure 2. Nonparametric regression curve for the association of height (cm), BMI at baseline (kg/m2), change in BMI since age 20 years (kg/m2), and non-occupational physical activity (min/day) with the chance of reaching longevity in men and women separately. Solid line represents point estimate and dashed lines represent 95% confidence intervals. All models were adjusted 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 (low, medium, high), energy intake (kcal, continuous), (A) Additionally adjusted for non-occupational

physical activity (≤30/ >30-60/ >60-90/ >90 min/day). P-value for non-linearity was 0.671 for men, and 0.211 for women. (B) Adjusted as in A. P-value for non-linearity was 0.572 in men, and <0.001 in women. (C) As in A, and additionally adjusted for BMI at age 20 years (in kg/m2, continuous). P-value for non-linearity was 0.567 in men, and 0.115 in women. (D) Additionally adjusted for BMI at baseline (<18.5, 28.5-25, 25-<30, 30+ kg/m2). P-value for non-linearity was 0.363 in men, and 0.003 in women.

In table 3, in men, a significant interaction was observed between smoking status and categorical BMI on reaching longevity (P-interaction=0.041). A BMI of ≥25 kg/m2 seemed to be inversely associated with reaching longevity in never- and former smokers, while a BMI ≥25kg/m2 was positively associated with reaching longevity in current smokers. However, a statistically significant effect estimate was only observed in former smokers. In analyses with BMI as a continuous variable no significant interaction was observed by smoking status (Table 3; P-interaction=0.128). In women, a significant interaction was observed between history of disease at baseline and categorical BMI (P-interaction=0.039). In women with a history of disease, the RR of reaching longevity with a BMI ≥25 kg/m2 was 0.67 (95%CI, 0.51-0.88), compared to women with a BMI <25 kg/m2. In women without a history of disease this association was weaker (RR, 0.95; 95%CI, 0.86-1.06) (Table 3). Regarding physical activity, in men we observed that the association between non-occupational physical activity with reaching longevity was significantly modified by BMI in continuous levels of non-occupational physical activity (p=0.023), but not in categorical physical activity. An inverse association between BMI at baseline and longevity was observed in men without a history of disease, but this relationship was non-significant (Figure 3).

Table 3: Multivariable-adjusted[a] RRs for reaching longevity according to BMI at baseline and non-occupational physical activity by strata of smoking status and disease history in birth cohorts of 1916-17; Netherlands Cohort Study (1986-2011).

	Body Mass index (kg/m^2)			Non-occupational physical activity					
	18.5-<25	≥25	Continuous	≤30	>30-60	>60-90	>90	*P*-trend	Continuous
Men									
Overall									
Survivors (90+)/n	254/1,404	176/1,161		69/569	137/794	88/489	139/739		
RR (95% CI)	1 (ref.)	0.88 (0.74-1.05)	0.98 (0.95-1.02)	1 (ref.)	1.34 (1.02-1.75)	1.28 (0.96-1.71)	1.39 (1.07-1.82)	0.036	1.02 (1.00-1.03)
Smoking status									
Never smokers									
Survivors (90+)/n	39/136	28/116		8/53	22/75	17/49	21/79		
RR (95% CI)	1 (ref.)	0.81 (0.54-1.21)	1.01 (0.93-1.10)	1 (ref.)	2.11 (1.01-4.41)	2.45 (1.16-5.18)	2.02 (0.97-4.22)	0.089	1.03 (1.01-1.06)
Former smokers									
Survivors (90+)/n	149/689	92/626		48/294	74/379	48/273	71/374		
RR (95% CI)	1 (ref.)	0.70 (0.55-0.89)	0.95 (0.90-0.99)	1 (ref.)	1.13 (0.81-1.58)	0.98 (0.68-1.41)	1.09 (0.79-1.52)	0.847	1.01 (0.99-1.03)
Current smokers									
Survivors (90+)/n	66/579	56/419		13/222	41/340	23/167	47/286		
RR (95% CI)	1 (ref.)	1.25 (0.90-1.74)	1.03 (0.97-1.09)	1 (ref.)	1.91 (1.04-3.49)	2.01 (1.05-3.85)	2.66 (1.46-4.85)	0.001	1.03 (1.01-1.05)
P-interaction		0.041	0.128				0.124		0.245
History of disease at baseline[c]									
No history of disease									
Survivors (90+)/n	201/890	130/720		47/318	111/524	63/300	112/482		
RR (95% CI)	1 (ref.)	0.85 (0.70-1.04)	0.97 (0.93-1.01)	1 (ref.)	1.37 (1.01-1.87)	1.28 (0.91-1.79)	1.45 (1.06-1.97)	0.048	1.02 (1.01-1.03)
History of disease									
Survivors (90+)/n	53/514	46/441		22/251	26/270	25/189	27/257		
RR (95% CI)	1 (ref.)	1.05 (0.71-1.56)	1.03 (0.96-1.11)	1 (ref.)	1.09 (0.64-1.86)	1.28 (0.75-2.20)	1.10 (0.65-1.85)	0.626	1.01 (0.98-1.04)
P-interaction		0.300	0.122				0.722		0.680

Body Mass Index (kg/m²)									
18.5-<25									
Survivors (90+)/n	NA	NA	NA	36/283	83/443	60/283	75/395		
RR (95% CI)	NA	NA	NA	1 (ref.)	1.37 (0.96-1.95)	1.46 (1.00-2.14)	1.38 (0.96-1.99)	0.121	1.01 (0.99-1.02)
≥25									
Survivors (90+)/n	NA	NA	NA	33/282	52/338	27/202	64/339		
RR (95% CI)	NA	NA	NA	1 (ref.)	1.29 (0.86-1.93)	0.97 (0.60-1.55)	1.39 (0.94-2.06)	0.195	1.03 (1.01-1.04)
P-interaction			NA				0.296		0.023
Women									
Overall									
Survivors (90+)/n	560/1,519	425/1,329		299/972	353/898	187/542	155/476		
RR (95% CI)	1 (ref.)	0.89 (0.80-0.99)	NA[d]	1 (ref.)	1.21 (1.07-1.37)	1.05 (0.90-1.22)	1.00 (0.85-1.17)	0.814	NA[c]
Smoking status									
Never smokers									
Survivors (90+)/n	407/1,043	324/968		229/690	258/641	141/381	112/328		
RR (95% CI)	1 (ref.)	0.88 (0.78-0.99)	NA[d]	1 (ref.)	1.16 (1.01-1.34)	1.06 (0.89-1.25)	0.96 (0.80-1.15)	0.677	NA[c]
Former smokers									
Survivors (90+)/n	86/240	66/213		40/143	57/147	26/91	29/76		
RR (95% CI)	1 (ref.)	0.92 (0.70-1.20)		1 (ref.)	1.33 (0.95-1.85)	0.95 (0.62-1.45)	1.31 (0.89-1.94)	0.457	NA[c]
Current smokers									
Survivors (90+)/n	67/236	35/148		30/139	38/110	20/70	14/72		
RR (95% CI)	1 (ref.)	0.92 (0.65-1.29)	NA[d]	1 (ref.)	1.60 (1.07-2.39)	1.37 (0.85-2.21)	0.89 (0.50-1.59)	0.835	NA[c]
P-interaction		0.823					0.491		
History of disease at baseline[c]									
No history of disease									
Survivors (90+)/n	454/1,120	359/937		248/675	288/662	158/398	127/356		
RR (95% CI)	1 (ref.)	0.95 (0.86-1.06)	NA[d]	1 (ref.)	1.14 (1.00-1.30)	1.04 (0.89-1.22)	0.94 (0.79-1.12)	0.458	NA[c]

History of disease									
Survivors (90+)/n	106/399	66/392		51/297	65/236	29/144	28/120		
RR (95% CI)	1 (ref.)	0.67 (0.51-0.88)	NA[d]	1 (ref.)	1.41 (1.02-1.94)	1.01 (0.67-1.52)	1.18 (0.79-1.77)	0.685	NA[e]
P-interaction		0.010					0.090		
Body Mass Index (kg/m^2)									
18.5-<25									
Survivors (90+)/n	NA	NA	NA	155/468	206/483	98/286	101/282		
RR (95% CI)	NA	NA	NA	1 (ref.)	1.24 (1.05-1.46)	0.99 (0.81-1.22)	1.04 (0.85-1.26)	0.775	NA[e]
≥25									
Survivors (90+)/n	NA	NA	NA	141/489	143/402	87/249	54/189		
RR (95% CI)	NA	NA	NA	1 (ref.)	1.20 (0.99-1.45)	1.14 (0.92-1.42)	0.97 (0.75-1.26)	0.831	NA[e]
P-interaction			NA				0.604		

[a] Model adjusted 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 (low, medium, high), energy intake (kcal, continuous), and non-occupational physical activity (≤30/ >30-60/ >60-90/ >90 min/day). [b] Excluding <18 kg/m2. [c] Diseases included; any type of cancer, heart attack, angina pectoris, cerebral hemorrhage, asthma, bronchitis, and diabetes. [d] Not applicable due to non-linearity between BMI at baseline and longevity. [e] Not applicable due to non-linearity between non-occupational physical activity and longevity.

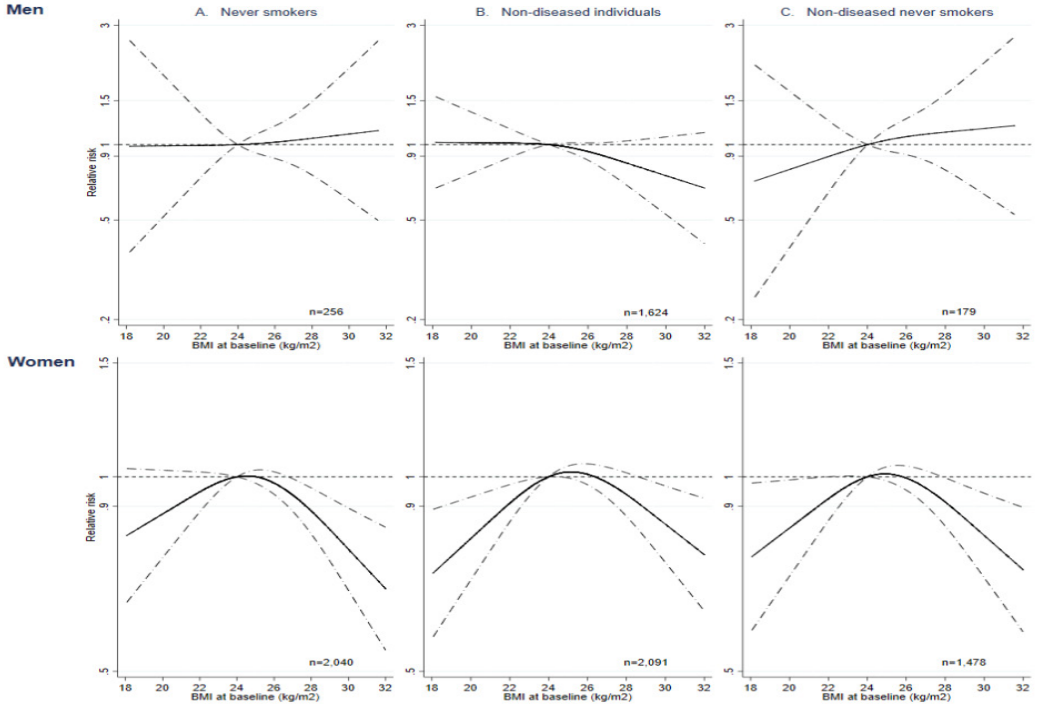

Figure 3: Nonparametric regression curve for the association between BMI at baseline (kg/m2), and the chance of reaching longevity in men and women separately. Restricted cubic spline regression analyses were performed using three knots at the 10th, 50th, and 90th percentile. Solid line represents point estimate and dashed lines represent 95% confidence intervals. All models were adjusted for age (years), alcohol consumption (0, 0.1-15, >15 g/day), educational level (low, medium, high), non-occupational physical activity energy intake (kcal, continuous), **(A)** P-value for non-linearity was 0.902 for men, and 0.002 for women. **(B)** Additionally adjusted for smoking status (never, former, current), number of cigarettes smoked per day (continuous, centered), smoking duration in years (continuous, centered). P-value for non-linearity was 0.413 in men, and <0.001 in women. **(C)** P-value for non-linearity was 0.775 in men, and 0.003 in women.

Discussion

In this large prospective cohort study, significant associations between reaching the age of 90 years and height, BMI at baseline (age 68-70 years), and an increase in BMI since the age of 20 years were observed in women, but not in men. In women, height was positively associated with reaching longevity. Significantly inverse associations were observed between reaching longevity and BMI at baseline, and BMI change since the age of 20 years. No significant associations between BMI at age 20 years and reaching longevity were found in both sexes. In men, a significantly linear positive dose-response relationship was found between increasing non-occupational physical activity and the chance of reaching longevity. In women, a significantly inverse U-shaped relationship was found between non-occupational physical activity and longevity, with the highest chance of reaching longevity around 60 minutes of non-occupational physical activity per day.

In our study, height was positively associated with the chance of reaching longevity in women, but not in men. In epidemiological studies, height is often positively associated with several types of cancer (26), and inversely associated with cardiovascular disease, diabetes, pulmonary disease, and mortality risk (27, 28), in both men and women. However, these findings have not always been consistent (29). Attained adult height is genetically determined as well an indicator for early-life circumstances, like energy intake, childhood infections, and socioeconomic status (30). Some studies suggest that childhood infections and nutritional deprivation in early-life may have long-lasting effects that express themselves in a shorter adult height and a higher risk for late-life diseases (31-35). In contrast, other researchers suggest that a shorter body stature actually increases lifespan, and that the observed inverse relationship between height and mortality is mainly caused by residual confounding of income, stress, and self-esteem (29, 36). Although it is still unclear whether height and longevity are associated, our results indicate that the underlying mechanisms may differ by sex. We can only speculate as to why height is differentially associated with reaching longevity between men and women in our study. Maybe, the observed relationship is related to shrinkage, which is more common in women during aging (37). However, no data was available to further investigate this relationship.

In men, we observed no significant associations between BMI and the chance of reaching longevity. In the Physicians' Health Study (PHS), it found that men aged 66 years and older with a BMI higher than 30kg/m2 had a significantly decreased chance of reaching 90 years (HR,0.69) compared to those with a BMI lower than 25kg/m2(9). No significant associations with longevity were observed for overweight men (HR,1.03) (9). Two other studies from the Honolulu Heath Program (HHP) and Iowa-ESEPE cohort, observed inverse but non-significant odds ratios (OR's) between reaching longevity, and overweight (≥25-<30 kg/m2) and obesity (≥30 kg/m2) compared to normal weight men (<25 kg/m2) (7, 10). However, these studies used other longevity cut-off ages (LCA) in men, 85 and 94 years respectively. In addition to studies on longevity, three literature reviews on BMI and mortality risk showed that a BMI ≥25kg/m2 in men was associated with an increased mortality

risk (38-40).

Although our results seem to differ from those of earlier studies, some study-specific characteristics may explain the observed differences. Firstly, 38% of the men included in our analyses had a history of (selected) disease at baseline, whereas diseased individuals were excluded from the longevity analyses in the PHS-, HHP- and Iowa-ESEPE cohorts. As shown in Figure 3, an inverse, but non-significant association was found between BMI and reaching longevity in non-diseased individuals. Although no significant modifying effect of disease status on the relationship between BMI and longevity was observed, diseased men might benefit from a higher BMI in terms of survival, in contrast to non-diseased men. Secondly, the men in our study had a relatively high baseline age (68-70 years). Two literature reviews of BMI and mortality have shown that the effect estimate between BMI and mortality became weaker at higher baseline ages (70-89 years) (38, 40). Future studies should investigate whether age and/or disease status in men might alter the association between BMI and reaching longevity.

In women, two cohort studies (Iowa-ESEPE: LCA, 97 and Gothenburg: LCA, 85) reported the association between BMI and reaching longevity (10, 11). Compared to normal weight women, in Iowa-ESEPE, a non-significantly decreased chance of reaching longevity was observed in overweight (25-<30 kg/m2) or obese (≥30 kg/m2) women, with corresponding ORs of 0.87, and 0.44, respectively. In the Gothenburg cohort, women in the two highest BMI quintiles (26.6-29.2 kg/m2 and 29.3-39.8 kg/m2) also showed non-significantly inverse associations with reaching longevity compared to the middle BMI quintile (24.6-26.5 kg/m2) (RR, 0.86 and RR, 0.80, respectively). Although the results of these studies were not statistically significant, the effect estimates are in line with results of our study, suggesting an adverse effect of overweight and obesity on the chance of reaching longevity in women. In addition to overweight and obesity, we observed an inverse but non-significant association between being underweight (<18.5 kg/m2) and reaching longevity in both sexes, but the sample size was small.

Not stratifying for smoking and disease status has often led to biased results on the relationship between BMI and mortality (38, 39). Current smokers and diseased individuals more often have a lower BMI, and a higher risk for mortality compared to never smokers and non-diseased individuals, respectively. As a result, the risk for mortality tends to be underestimated in overweight individuals, while overestimated in underweight individuals when not stratifying for these factors. Only one longevity study, that of the Oslo Ischemia Study (OIS) (LCA, 85), has stratified for smoking status, but only in men (6). It found that men with overweight or obesity at ages 51-59 years had a significantly lower chance of reaching the age of 85 compared to men with lower weight (BMI <25kg/m2), but only in non-smokers (6).

In our study, smoking status in men acted as a significant effect-modifier between categories of BMI at baseline and longevity (P=0.041). However, additional continuous analyses, showed no significant interaction between smoking status and

BMI per 1 kg/m2 increase in men. As a result, the potential modifying effect of smoking on the relationship between BMI and longevity in men remains unclear. In women, no significant interaction by smoking status was observed.
In men, we observed no significantly modifying effect of disease history on the relationship between BMI and longevity. In women, a history of (selected) disease at baseline seems to act as a potential effect-modifier. The association between being overweight and reaching longevity seems to be stronger in women with a history of (selected) disease compared to women without a history of disease. These results indicate that not stratifying by smoking- and disease status when studying the association between BMI and longevity might also lead to biased results. Furthermore, the potential modifying effect by smoking and disease history seems to differ by sex.

In our study, we observed a positive linear dose-response relationship between non-occupational physical activity and reaching longevity in men (Figure 2). In women, we observed an inverse U-shaped relationship between physical activity and longevity with the highest likelihood of reaching longevity around 60min/day (Figure 2). One analysis from the PHS cohort investigated a dose-response relationship between different levels of physical activity and the chance of reaching longevity (90 years) in men (9). As in our study, it found a significant positive association with longevity at a low level of physical activity (1-4 times/month) (HR,1.28), but the effect estimate did not increase further in higher levels of physical activity. In a European study (PAQUID), the association between regular exercise (yes/no) and reaching 90 years was somewhat stronger in men compared to women (HR,1.35 vs. HR,1.12), which is in line with the results of our study(15).

Although the dose-response relation between physical activity and longevity in our study seems to differ between both sexes, no significant effect-modification by sex was observed (Table 2). This leaves open the possibility that the observed differences are due to chance. Furthermore, no information was available on the intensity level of physical activity (e.g. moderate, vigorous) for these analyses. However, in studies on mortality, it has been suggested that the beneficial effect of a higher intensity level is counterbalanced by an increased risk on mortality due to cardiovascular side-effects (41). This decreases the probability that the intensity level has influenced our results.

Strengths of this study are the prospective design, 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. Firstly, information on weight has only been collected at baseline measurement, and retrospectively for the age of 20 years. Secondly, our exposure variables were self-reported. This might have led to some under- or overestimation, depending on the exposure of interest. Thirdly, the potential problem of reverse causation arises as well. Although we collected

information on disease status at baseline, some baseline characteristics might be explained by the participants' preclinical disease status (i.e. weight and physical activity). Lastly, the diseases selected for our additional analyses were restricted to the most important non-communicable diseases that are associated with premature mortality, and BMI and/or physical activity (42-49). Therefore, "history of selected diseases" is no direct indication for a participants' health status.

Our findings showed that height, BMI at age 68-70 years, and BMI change since the age of 20 years were significantly associated with reaching longevity in women, but not in men. Non-occupational physical activity was positively significantly associated with an increased chance of reaching longevity in both sexes, but evidence for a non-linear relationship was observed in women.

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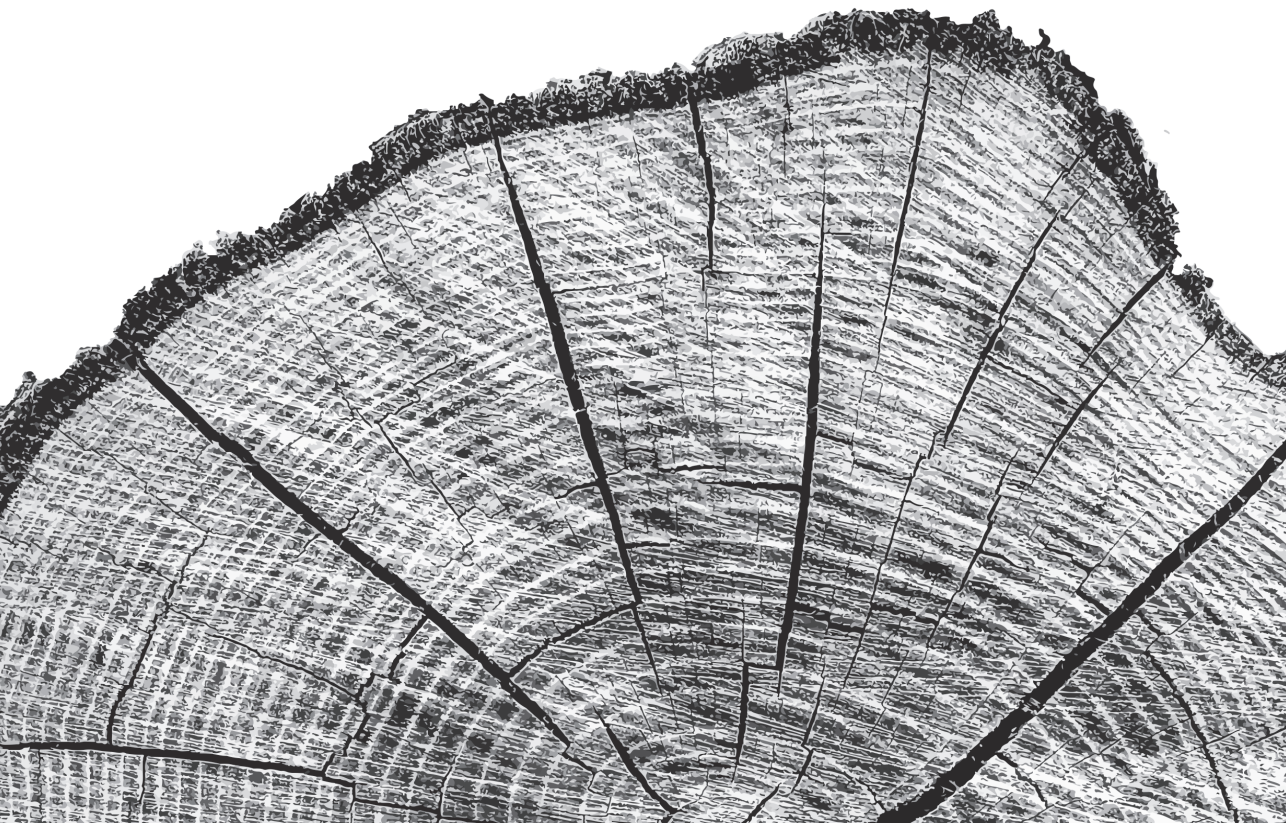
Chapter 6

Alcohol consumption in later life and reaching longevity: the Netherlands Cohort Study

Piet A. van den Brandt, and Lloyd Brandts

Age and Ageing. May 2020; 49(3): 395-402



Alcohol consumption in later life and reaching longevity: the Netherlands Cohort Study

Piet A. van den Brandt, Lloyd Brandts

Abstract

Background:
Whether light to moderate alcohol intake is related to reduced mortality remains a subject of intense research and controversy. There are very few studies available on alcohol and reaching longevity.
Methods
We investigated the relationship of alcohol drinking characteristics with the probability to reach 90 years of age. Analyses were conducted using data from the Netherlands Cohort Study. Participants born in 1916–1917 (n=7807) completed a questionnaire in 1986 (age 68–70 years) and were followed up for vital status until the age of 90 years (2006–2007). Multivariable Cox regression analyses with fixed follow-up time were based on 5479 participants with complete data to calculate risk ratios (RRs) of reaching longevity (age 90 years).
Results
We found statistically significant positive associations between baseline alcohol intake and the probability of reaching 90 years in both men and women. Overall, the highest probability of reaching 90 was found in those consuming 5-<15 g/d alcohol, with RR=1.36 (95% CI, 1.20-1.55) when compared with abstainers. The exposure-response relationship was significantly nonlinear in women, but not in men. Wine intake was positively associated with longevity (notably in women), whereas liquor was positively associated with longevity in men and inversely in women. Binge drinking pointed towards an inverse relationship with longevity. Alcohol intake was associated with longevity in those without and with a history of selected diseases.
Conclusions
The highest probability of reaching 90 years was found for those drinking 5-<15 g alcohol/day. Although not significant, the risk estimates also indicate to avoid binge drinking.

Introduction

Whether light to moderate alcohol intake is related to reduced mortality remains a subject of intense research and controversy, e.g. (1, 2). Whereas alcohol consumption has been studied frequently in relation to mortality (especially CVD), the findings were inconsistent. Many studies have reported J-shaped curves relating alcohol to mortality suggesting the lowest risk for light-moderate drinkers (2-5), while others found nonsignificant associations or linear associations (1, 6, 7). Many early cohort studies may have suffered from "abstainer bias" where ex-drinkers are misclassified as abstainers and related inclusion of subjects with chronic diseases (sick quitters), and limited confounder adjustment (5, 6, 8). A recent meta-analysis addressing these issues (6) found no protective effect of low-moderate drinking in the subset of studies that controlled for these biases, but this selection was criticized (9). While mortality studies investigate risk factors for premature death (i.e. earlier than average), longevity studies investigate determinants of attaining exceptionally high ages (exceeding life expectancy). The relationship between alcohol and longevity has been investigated rarely, with survival cut-off ages of 85 (10, 11) or younger (12) in early cohort studies, and 90 in recent studies (13, 14). Furthermore, most studies involved men only (10, 11, 13), did not exclude ex-drinkers and results were inconsistent.

We investigated the relationship between habitual alcohol intake in later life and the probability of reaching 90 years in men and women (because alcohol affects women differently from men (15)), within the Netherlands Cohort Study (NLCS). Given the controversies surrounding light-to-moderate alcohol intake and mortality, we concentrated on this category in dose-response modelling. We also aimed to investigate beverage types, stability of drinking over time and effect of excluding ex-drinkers, and binge drinking, because these factors were important in mortality studies.

Methods

Study design and population

For this study, data from the ongoing NLCS was used. The NLCS started in September 1986 as a large population-based prospective study, with detailed information on baseline alcohol use and many confounders available from men and women (16, 17). Eligible subjects were men and women living in 204 Dutch municipalities, aged 55-70 years at cohort baseline (1986). NLCS-participants born in 1916-1917 were selected to form the longevity cohort for the current analyses (i.e. aged 68-70 at baseline), because younger birth cohorts could not have reached age 90 at the end of follow-up (14, 18). Vital status follow-up consisted of record linkage to the Central Bureau for Genealogy and to municipal population registries from 1986-2007, yielding exact dates of death. Vital status follow-up of the longevity cohort until age 90 (2006-2007) was 99.9% complete; seven participants were lost to follow-up due to migration. The resulting study population consisted of 3,646 men and 4,161 women (Figure 1).

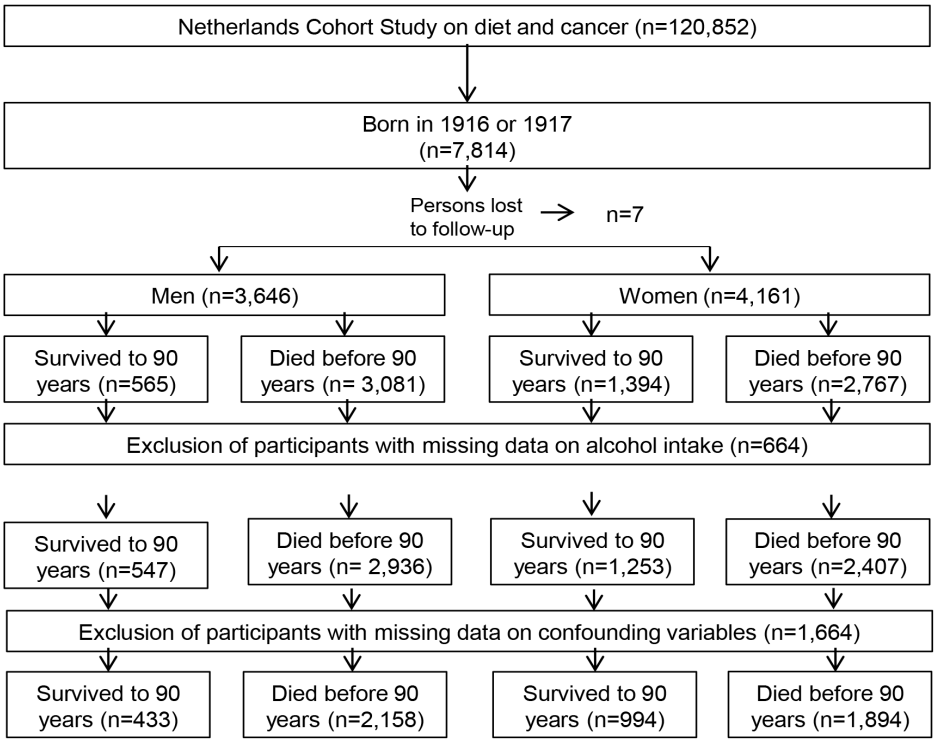


Figure 1: Flow diagram on analyses of alcohol intake and longevity in birth cohorts 1916-17, Netherlands Cohort Study (1986-2007).

Exposure assessment
The 11-page baseline questionnaire measured dietary intake, detailed information on lifestyle factors, and medical conditions (16). Habitual consumption of food and (alcoholic) beverages during the year preceding baseline was assessed using a semi-quantitative food-frequency questionnaire (FFQ), which was validated against a 9-day diet record (19).

Consumption of alcoholic beverages was addressed by questions on beer, red wine, white wine, sherry and other fortified wines, liqueur types containing on average 16% ethanol, and (Dutch) gin, brandy, and whiskey. Respondents who consumed alcoholic beverages less than once a month were considered non-users. Four items from the questionnaire (i.e. red wine, white wine, sherry, and liqueur) were combined into one wine variable, since these items were substantially correlated (20). Mean daily alcohol consumption was calculated using the Dutch food composition table (21). The FFQ has been validated and tested for reproducibility (19, 22). For mean daily ethanol intake, Spearman correlation coefficients between

the 9-day diet record and the questionnaire were 0.89 for all subjects and 0.85 for alcohol users (19). The absolute amount of ethanol reported in the questionnaire by alcohol users was, on average, 86% of that reported in the 9-day diet record (19).

The baseline questionnaire also asked about the usual pattern of drinking alcoholic beverages (parties only/ weekend & parties/ throughout week). To measure binge drinking, subjects were asked how often they drank more than 6 alcoholic drinks per occasion during the half year preceding baseline. Finally, a question provided information on the subjects' drinking habits five years before baseline. Ex-drinkers were defined as participants who were not drinking alcohol at baseline, but who drank alcoholic beverages 5 years before baseline.

Statistical analyses
Subjects with missing data on alcohol and confounding variables were excluded. The associations of alcohol consumption, alcoholic beverages and drinking characteristics with the probability of reaching 90 years (longevity) were estimated in age(-sex) and multivariable-adjusted analyses using Cox regression models with a fixed follow-up time (18, 23), in categorical and continuous exposure analyses, correcting for potential confounders (related to longevity and alcohol (see footnotes in Tables)). Standard errors were calculated using the Huber-White sandwich estimator (24). Ex-drinkers were excluded from the main analyses to avoid misclassification of ex-drinkers as abstainers. Beverage-specific analyses for beer, wine and liquor were additionally mutually adjusted to evaluate the association of each beverage with longevity independently of other alcoholic beverages. Analyses of the effect of pattern of drinking, and binge drinking were additionally adjusted for total intake of alcoholic beverages.

Tests for trends were assessed using Wald tests, by fitting median values of intake per intake category as continuous terms. Restricted cubic spline regression analyses using four knots (at the midpoints of the categories used in categorical analyses), and Wald test were performed to test for non-linearity. We conducted sensitivity analyses, by restricting analyses to participants who reported to have had the same alcohol intake five years before baseline, including abstainers on both occasions (i.e., the stable subgroup). To evaluate potential residual confounding by other risk factors, and effect modification, analyses of alcohol and longevity were also conducted within strata of covariables. Interactions were tested using Wald tests and cross-product terms. Analyses were performed using Stata 14; presented P-values are two-sided.

Results
Among the 2591 men, 433 (16.7%) survived until 90 years, and there were 994 survivors (34.4%) among the 2888 women. In the total group, 40 men and 32 women were ex-drinkers. When excluding ex-drinkers, the proportion of alcohol abstainers was higher among non-survivors than survivors in both men (15.6% versus 10.6%) and women (37.4% and 30.1%). Among male alcohol consumers, mean intake (SD) was 16.5 (15.8) g/day in non-survivors and 15.9 (14.9) g/

day in survivors. For women these numbers were 8.0 (10.5) and 7.2 (9.0) g/day, respectively. Table 1 also shows these comparisons for beverage types (glasses/week), pattern of drinking, stable drinking, and binge drinking. The proportion of binge drinkers was higher among non-survivors than survivors, and higher in men: 18.5% versus 14.2% in men, and 6.1% versus 4.0% in women, respectively. Alcohol consumption was positively associated with smoking, educational level and energy intake in both sexes, with physical activity in women, and with BMI and height in men (Table 2). There was no clear association with history of selected diseases. Ex-drinkers more often had a history of selected diseases than those in other drinking categories. Excluded subjects with missings had a lower likelihood of reaching 90, were less often smokers and less highly educated (Table 3).

Alcohol intake was positively associated with the probability of reaching 90 years in men and women in multivariable-adjusted analyses (Table 4). In analyses of men and women combined, those drinking 5-<10 g alcohol/day had a RR of 1.41 (95%CI, 1.21-1.63) of reaching 90, compared to abstainers. This probability remained elevated at higher alcohol intake levels (P-trend= 0.014). Ex-drinkers had a decreased probability of reaching 90, when compared to abstainers. Ex-drinkers were excluded from subsequent analyses. When alcohol was analyzed as continuous variable, the RR per increment of 10 g/d was 1.05 (95%CI 1.01-1.09). In analyses limited to the stable subgroup, similar associations were seen as in the overall group. There was no statistically significant interaction between men and women (p=0.168). However, the estimated associations showed differences: whereas in men the probability of reaching 90 remained elevated at higher alcohol consumption levels (e.g., RR=1.64 (1.15-2.34) for men drinking 30+g/day compared to abstainers), this was not seen in women with: RR=0.99 (0.69-1.44). This difference in dose-response was also noticed in restricted cubic splines analyses, where a significantly nonlinear relationship was observed in women (p for nonlinearity= 0.004), but not in men (Figure 2). We therefore continued with sex-specific analyses.

In beverage-specific analyses, we found no association with beer intake (Table 5). Wine intake was associated with higher chances of reaching 90 among women, with RRs of 1.43 (95%CI 1.21-1.68) and 1.35 (1.14-1.59) for women drinking 3.5-<7 and 7+ glasses/week, respectively, when compared to nondrinkers of wine (p-trend <0.001, and p-trend= 0.049 among wine drinkers). For men, the weakly positive associations with wine were nonsignificant. Liquor intake was significantly positively associated with longevity among men in several drinking categories compared to nondrinkers of liquor, but the trend test and continuous analyses were not significant. In women, however, higher liquor intake was inversely associated with longevity (p-trend= 0.044, and p-trend= 0.018 among liquor drinkers).

Table 1. Baseline characteristics of the cohort members by survival (90+ years) status in birth cohorts 1916-17; Netherlands Cohort Study (1986-2007).

	Men				Women			
	Died before 90		Survived to age 90		Died before 90		Survived to age 90	
	N	%	N	%	N	%	N	%
N	2158		433		1894		994	
ALL (including non-drinkers)								
Alcohol intake categories								
Ex, 0 g/d	34	1.6	6	1.4	27	1.4	5	0.5
0 g/day (abstainer)	337	15.6	46	10.6	709	37.4	299	30.1
0.1-<5	512	23.7	106	24.5	691	36.5	401	40.3
5-<10	260	12.0	75	17.3	156	8.2	106	10.7
10-<15	280	13.0	52	12.0	109	5.8	79	7.9
15-<30	443	20.5	84	19.4	133	7.0	82	8.2
30+	292	13.5	64	14.8	69	3.6	22	2.2
Alcohol consumers	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	
Alcohol (g/day); mean (SD)	16.5 (15.8)		15.9 (14.9)		8.0 (10.5)		7.2 (9.0)	
Beer (glasses/week); mean (SD)	2.2 (4.6)		2.0 (4.3)		0.1 (0.8)		0.1 (0.8)	
Wine incl sherry, liqueur (glasses/week); mean (SD)	2.9 (5.6)		3.3 (5.4)		4.0 (5.6)		4.2 (5.1)	
Liquor (glasses/week); mean (SD)	5.2 (6.7)		4.7 (6.2)		1.0 (3.0)		0.5 (2.0)	
	N	%	N	%	N	%	N	%
Change in alcohol consumption in last 5 years								
Stable	1060	68.4	260	76.9	636	77.1	393	76.2

Moderated	302	19.5	48	14.2	115	13.9	66	12.8
Increased	187	12.1	30	8.9	74	9.0	57	11.0
Type of alcoholic beverage								
Only beer	90	5.1	14	3.7	13	1.1	5	0.7
Only wine	269	15.1	58	15.3	851	73.9	536	78.1
Only liquor	288	16.2	54	14.2	47	4.1	15	2.2
Beer and wine	156	8.8	37	9.8	63	5.5	45	6.6
Wine and liquor	272	15.3	63	16.6	134	11.6	66	9.6
Beer and liquor	274	15.4	44	11.6	9	0.8	2	0.3
Beer, wine and liquor	433	24.3	109	28.8	34	3.0	17	2.5
Pattern of alcohol drinking								
Only at parties	301	18.4	64	18.2	320	32.8	179	30.3
Weekend and parties	501	30.6	124	35.2	334	34.2	224	37.9
Throughout the week	836	51.0	164	46.6	322	33.0	188	31.8
Frequency of 7+ drinks/occasion in last 6 months								
0 times/ last 6 months	1127	81.5	260	85.8	749	93.9	437	96.0
1-<2 times	52	3.8	13	4.3	19	2.4	7	1.5
2-<3 times	45	3.3	8	2.6	10	1.3	2	0.4
3-<5 times	59	4.3	6	2.0	8	1.0	4	0.9
5 times or more	100	7.2	16	5.3	12	1.5	5	1.1

Binge drinking (7+ drinks/occasion) in last 6 months								
No	1127	81.5	260	85.8	749	93.9	437	96.0
Yes	256	18.5	43	14.2	49	6.1	18	4.0

Table 2. Baseline characteristics (means or percent) according to alcohol consumption level in men and women with complete dietary and covariable data, NLCS 1916-1917 birth cohorts.

Characteristic	Alcohol consumption (g/day)						
	0	0.1-<5	5-<10	10-<15	15-<30	30+	*Ex, 0 g/d*
Men							
N	383	618	335	332	527	356	*40*
Median alcohol intake(g/day)	0	2.1	7.4	12.1	22.4	40.6	*0*
BMI (kg/m^2); mean	24.4	24.8	24.7	25.1	25.0	25.2	*24.4*
Height (cm), mean	174.7	174.9	175.0	174.9	175.0	175.6	*175.1*
Physical activity, nonocc. (min/day); mean	73.0	77.5	71.2	74.9	75.6	71.5	*74.0*
Energy intake (kcal/day); mean	1969	1968	2013	2095	2083	2180	*1985*
Never smoker (%)	20.9	13.1	11.0	6.9	4.7	2.0	*7.5*
University or higher vocational education (%)	13.1	14.6	17.3	17.5	18.2	29.8	*7.5*
History of (selected) diseases[a] (% yes)	47.8	41.6	42.1	49.4	45.0	38.5	*57.5*
Women							
N	1008	1092	262	188	215	91	*32*
Median alcohol intake(g/day)	0	1.4	7.2	12.1	20.7	35.6	*0*
BMI (kg/m^2); mean	25.2	25.2	25.0	24.4	24.6	24.1	*25.5*

Height (cm), mean	164.0	164.1	164.4	164.3	164.4	163.1	*165.1*
Physical activity, nonocc. (min/day); mean	52.1	57.4	57.0	58.6	57.8	59.8	*56.3*
Energy intake (kcal/day); mean	1615	1643	1700	1723	1693	1722	*1672*
Never smoker (%)	82.1	74.9	64.1	51.1	41.9	23.1	*59.4*
University or higher vocational education (%)	5.6	7.2	13.4	12.2	13.5	12.1	*15.6*
History of (selected) diseases[a] (% yes)	52.7	47.1	45.4	39.9	40.5	44.0	*56.3*

[a] Physician-diagnosed myocardial infarction, angina pectoris, stroke, cancer (excluding skin cancer), diabetes or hypertension.

Table 3. Baseline characteristics (means or percent) and survival for excluded subjects due to missings on alcohol or covariables in men and women, NLCS 1916-1917 birth cohort.

Characteristic	Excluded: Missing alcohol intake	Excluded: Missing covariables	Included: No missings
Men			
N	163	892	2591
Median alcohol intake(g/day)	-	12.2	13.7
BMI (kg/m^2); mean	24.9	-	24.8
Height (cm), mean	172.9	-	175.0
Physical activity, nonocc. (min/day); mean	69.3	-	74.4
Energy intake (kcal/day); mean	1828	-	2042
Never smoker (%)	15.3	-	9.9
University or higher vocational education (%)	6.1	-	17.8
History of (selected) diseases[a] (% yes)	40.5	-	44.1
Survived to age 90 (%)	11.0	12.8	16.7
Women			
N	501	772	2888
Median alcohol intake(g/day)	-	4.5	4.9
BMI (kg/m^2); mean	25.3	-	25.1
Height (cm), mean	163.9	-	164.1
Physical activity, nonocc. (min/day); mean	44.0	-	55.7
Energy intake (kcal/day); mean	1549	-	1650
Never smoker (%)	83.7	-	70.6
University or higher vocational education (%)	0.2	-	8.2
History of (selected) diseases[a] (% yes)	52.7	-	47.9
Survived to age 90 (%)	28.1	33.6	34.4

[a] Physician-diagnosed myocardial infarction, angina pectoris, stroke, cancer (excluding skin cancer), diabetes or hypertension.

Table 4. Age- and multivariable-adjusted[a] RRs for reaching longevity according to alcohol intake in birth cohort 1916-17; Netherlands Cohort Study (1986-2007).

		Alcohol (g/day)								
	Ex, 0 g/d	Abstainers	>0-<5 g/d	5-<10 g/d	10-<15 g/d	15-<30 g/d	30+ g/d	P for trend[b]	Continuous[b], per 10 g/d	P for inter-action[b]
Men and women										
Overall										
Median intake (g/day)	*0.0*	0.0	1.6	7.2	12.1	21.4	39.5			
N	*72*	1391	1710	597	520	742	447			
Survivors(90+)	*11*	345	507	181	131	166	86			
Age-sex-adjusted RR	*0.74*	1	1.26	1.49	1.32	1.24	1.15	0.391	1.01	
(95 %CI)	*(0.43 - 1.30)*	(Ref.)	(1.13 - 1.42)	(1.28 - 1.73)	(1.11 - 1.56)	(1.06 - 1.46)	(0.93 - 1.43)		(0.97 - 1.05)	
Multivariable-adjusted RR[a]	*0.84*	1	1.19	1.41	1.30	1.29	1.31	0.014	1.05	0.168
(95 %CI)	*(0.48 - 1.47)*	(Ref.)	(1.07 - 1.33)	(1.21 - 1.63)	(1.10 - 1.55)	(1.10 - 1.52)	(1.06 - 1.63)		(1.01 - 1.09)	
Stable subgroup										
Median intake (g/day)		0.0	1.8	7.2	12.1	22.0	40.0			
N		1180	907	364	319	467	292			
Survivors(90+)		288	287	114	83	109	60			
Age-sex-adjusted RR		1	1.37	1.52	1.34	1.28	1.18	0.364	1.01	
(95 %CI)		(Ref.)	(1.20 - 1.57)	(1.27 - 1.82)	(1.09 - 1.64)	(1.05 - 1.55)	(0.92 - 1.52)		(0.97 - 1.06)	
Multivariable-adjusted RR[a]		1	1.25	1.42	1.30	1.31	1.36	0.024	1.05	0.468
(95 %CI)		(Ref.)	(1.09 - 1.43)	(1.18 - 1.70)	(1.05 - 1.60)	(1.08 - 1.59)	(1.05 - 1.76)		(1.00 - 1.11)	
Men										
Median intake (g/day)	*0.0*	0.0	2.1	7.4	12.1	22.4	40.6			
N	*40*	383	618	335	332	527	356			

Survivors(90+)	*6*	46	106	75	52	84	64		
Age-adjusted RR	*1.24*	1	1.43	1.86	1.31	1.33	1.50	0.453	1.01
(95 %CI)	*(0.56 - 2.72)*	(Ref.)	(1.04 - 1.97)	(1.33 - 2.61)	(0.90 - 1.89)	(0.95 - 1.86)	(1.06 - 2.13)		(0.96 - 1.07)
Multivariable-adjusted RR[a]	*1.49*	1	1.39	1.81	1.37	1.43	1.64	0.100	1.04
(95 %CI)	*(0.69 - 3.23)*	(Ref.)	(1.01 - 1.90)	(1.30 - 2.53)	(0.95 - 1.97)	(1.02 - 1.99)	(1.15 - 2.34)		(0.98 - 1.10)
Women									
Median intake (g/day)	*0.0*	0.0	1.4	7.2	12.1	20.7	35.6		
N	*32*	1008	1092	262	188	215	91		
Survivors(90+)	*5*	299	401	106	79	82	22		
Age-adjusted RR	*0.53*	1	1.24	1.36	1.42	1.29	0.81	0.526	1.01
(95 %CI)	*(0.23 - 1.18)*	(Ref.)	(1.09 - 1.40)	(1.14 - 1.62)	(1.17 - 1.72)	(1.06 - 1.56)	(0.56 - 1.19)		(0.96 - 1.07)
Multivariable-adjusted RR[a]	*0.62*	1	1.17	1.28	1.38	1.31	0.99	0.078	1.05
(95 %CI)	*(0.27 - 1.38)*	(Ref.)	(1.03 - 1.32)	(1.08 - 1.52)	(1.13 - 1.68)	(1.08 - 1.60)	(0.69 - 1.44)		(0.99 - 1.11)

[a] Multivariable analyses were adjusted for: age at baseline (continuous, in years), tobacco smoking status (coded as never, former, current smoker), number of cigarettes smoked per day, and years of smoking (both continuous, centered)), body height (continuous, m), BMI (<18.5, 18.5-<25, 25-<30, ≥30 kg/m2), non-occupational physical activity (<30, 30-60, 61-90, ≥90 min/day), history of selected diseases at baseline (physician-diagnosed myocardial infarction, angina pectoris, stroke, cancer (excluding skin cancer), diabetes and hypertension; categorized as 0,1,2,3+ diseases), highest level of education (primary school or lower vocational, secondary or medium vocational, and higher vocational or university), energy intake (continuous, kcal/day). [b] Excluding ex-drinkers.

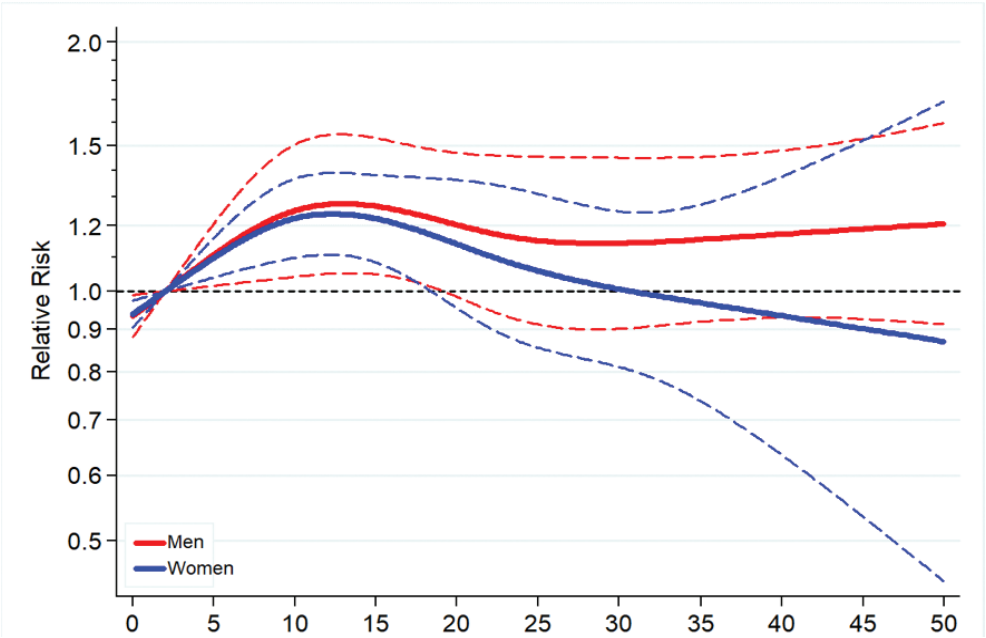


Figure 2. Spline regression curves for the association of alcohol consumption with the probability of reaching longevity in men and women separately. Red lines: men. Blue lines: women. Solid lines represents point estimates and dashed lines represent 95% confidence intervals. Multivariate HRs are calculated by restricted cubic spline regression adjusting for: age at baseline (continuous, in years), tobacco smoking status (coded as never, former, current smoker), number of cigarettes smoked per day, and years of smoking (both continuous, centered)), body height (continuous, m), BMI (<18.5, 18.5-<25, 25-<30, ≥30 kg/m2), non-occupational physical activity (<30, 30-60, 61-90, ≥90 min/day), history of selected diseases at baseline (physician-diagnosed myocardial infarction, angina pectoris, stroke, cancer (excluding skin cancer), diabetes and hypertension; categorized as 0,1,2,3+ diseases), highest level of education (primary school or lower vocational, secondary or medium vocational, and higher vocational or university), energy intake (continuous, kcal/day).

Table 5. Age- and multivariable-adjusted RRs for reaching longevity according to intake of specific alcoholic beverages in birth cohort 1916-17; Netherlands Cohort Study (1986-2007)

	Men							Women						
Alcoholic beverage	Median (gl/wk)	N	90+	RR[a]	(95% CI)	RR[b]	(95% CI)	Median (gl/wk)	N	90+	RR[a]	(95% CI)	RR[b]	(95% CI)
Beer (glasses/week)														
No	0.0	1388	221	1	(reference)	1	(reference)	0.0	2665	919	1	(reference)	1	(reference)
>0-<3.5	1.0	764	144	1.18	(0.98 - 1.43)	1.03	(0.85 - 1.25)	0.5	173	63	1.06	(0.86 - 1.30)	1.00	(0.82 - 1.22)
3.5-<7	5.0	198	33	1.05	(0.75 - 1.46)	1.00	(0.71 - 1.39)	5.0	13	6	1.33	(0.74 - 2.41)	1.22	(0.70 - 2.12)
7+ gl/wk	13.0	201	29	0.91	(0.63 - 1.29)	0.92	(0.64 - 1.31)	13.0	5	1	0.58	(0.10 - 3.32)	0.61	(0.09 - 4.09)
P for trend				0.493		0.611					0.970		0.857	
P trend, beer drinkers				0.140		0.545					0.768		0.913	
Continuous, per 7 gl/wk		2551	427	0.98	(0.85 - 1.13)	1.01	(0.86 - 1.18)		2856	989	1.00	(0.59 - 1.70)	0.97	(0.55 - 1.73)
P for interaction by sex													0.739	
Wine (glasses/week)														
No	0.0	1149	159	1	(reference)	1	(reference)	0.0	1099	321	1	(reference)	1	(reference)
>0-<3.5	1.0	881	167	1.37	(1.12 - 1.67)	1.17	(0.95 - 1.44)	1.0	1135	413	1.25	(1.10 - 1.40)	1.16	(1.03 - 1.30)
3.5-<7	5.0	236	49	1.50	(1.12 - 2.00)	1.15	(0.85 - 1.55)	5.1	265	116	1.50	(1.27 - 1.77)	1.43	(1.21 - 1.68)
7+ gl/wk	13.0	285	52	1.32	(0.99 - 1.76)	1.08	(0.81 - 1.46)	13.0	357	139	1.33	(1.14 - 1.56)	1.35	(1.14 - 1.59)
P for trend				0.087		0.880					0.001		<0.001	
P trend, wine drinkers				0.825		0.400					0.287		0.049	

Continuous, per 7 gl/wk		2551	427	1.08	(0.99 - 1.19)	1.04	(0.94 - 1.16)		2856	989	1.09	(1.02 - 1.16)	1.11	(1.04 - 1.19)
P for interaction by sex													0.555	
Liquor (glasses/ week)														
No	0.0	1011	156	1	(reference)	1	(reference)	0.0	2531	889	1	(reference)	1	(reference)
>0-<3.5	1.2	603	120	1.29	(1.04 - 1.60)	1.34	(1.08 - 1.67)	1.0	185	70	1.08	(0.89 - 1.31)	1.02	(0.85 - 1.24)
3.5-<7	5.0	365	55	0.98	(0.74 - 1.30)	1.12	(0.83 - 1.49)	6.5	81	19	0.67	(0.45 - 0.99)	0.72	(0.49 - 1.07)
7+ gl/wk	13.0	572	96	1.09	(0.86 - 1.37)	1.30	(1.02 - 1.66)	13.0	59	11	0.53	(0.31 - 0.91)	0.67	(0.40 - 1.15)
P for trend				0.956		0.172					0.003		0.044	
P trend, liquor drinkers				0.257		0.919					0.003		0.018	
Continuous, per 7 gl/wk		2551	427	0.97	(0.89 - 1.07)	1.05	(0.95 - 1.16)		2856	989	0.69	(0.54 - 0.89)	0.78	(0.60 - 1.01)
P for interaction by sex													0.062	

[a] Age-adjusted analyses. [b] Multivariable analyses were adjusted for: age at baseline (continuous, in years), tobacco smoking status (coded as never, former, current smoker), number of cigarettes smoked per day, and years of smoking (both continuous, centered)), body height (continuous, m), BMI (<18.5, 18.5-<25, 25-<30, ≥30 kg/m2), non-occupational physical activity (<30, 30-60, 61-90, ≥90 min/day), history of selected diseases at baseline (physician-diagnosed myocardial infarction, angina pectoris, stroke, cancer (excluding skin cancer), diabetes and hypertension; categorized as 0,1,2,3+ diseases), highest level of education (primary school or lower vocational, secondary or medium vocational, and higher vocational or university), energy intake (continuous, kcal/day), intake of the other 2 types of alcoholic beverages (each categorical).

Table 6. Age- and multivariable-adjusted RRs for reaching longevity according to alcohol drinking characteristics in drinkers, birth cohorts 1916-17; Netherlands Cohort Study (1986-2007).

Drinking characteristic	Men							Women						
	Median (gl/wk)	N	90+	RR[a]	(95% CI)	RR[b]	(95% CI)	Median (gl/wk)	N	90+	RR[a]	(95% CI)	RR[b]	(95% CI)
Pattern of alcohol drinking														
Only at parties	1.4	365	64	1	(reference)	1	(reference)	0.9	499	179	1	(reference)	1	(reference)
Weekend and parties	4.5	625	124	1.14	(0.87 - 1.50)	1.18	(0.90 - 1.55)	2.2	558	224	1.12	(0.96 - 1.30)	1.10	(0.95 - 1.28)
Throughout the week	14.0	1000	164	0.94	(0.73 - 1.23)	0.97	(0.71 - 1.32)	10.7	510	188	1.03	(0.87 - 1.21)	1.10	(0.89 - 1.36)
P for trend				0.360		0.736					0.759		0.277	
P for interaction with alcohol						0.979							0.105	
Binge drinking in last 6 months														
No	6.5	1387	260	1	(reference)	1	(reference)	2.4	1186	437	1	(reference)	1	(reference)
Yes	14.2	299	43	0.76	(0.57 - 1.03)	0.91	(0.66 - 1.26)	7.5	67	18	0.74	(0.49 - 1.10)	0.80	(0.53 - 1.20)
P for interaction with alcohol						0.080							0.404	
How often 7+ drinks/occasion in last 6 months														
0 times/ last 6 months	6.5	1387	260	1	(reference)	1	(reference)	2.4	1186	437	1	(reference)	1	(reference)
1-<2 times	11.9	65	13	1.06	(0.65 - 1.75)	1.22	(0.76 - 1.96)	2.2	26	7	0.73	(0.39 - 1.39)	0.69	(0.37 - 1.31)
2-<3 times	13.0	53	8	0.80	(0.42 - 1.53)	0.97	(0.51 - 1.84)	8.2	12	2	0.46	(0.13 - 1.64)	0.61	(0.19 - 1.96)
3-<5 times	13.5	65	6	0.49	(0.23 - 1.06)	0.58	(0.27 - 1.24)	8.8	12	4	0.92	(0.41 - 2.06)	1.04	(0.45 - 2.38)
5 times or more	21.0	116	16	0.73	(0.46 - 1.17)	0.88	(0.51 - 1.49)	26.7	17	5	0.81	(0.39 - 1.68)	0.98	(0.45 - 2.12)

P for trend	0.044	0.345		0.266	0.605
P for interaction with alcohol		0.510			0.147

[a] Age-adjusted analyses [b] Multivariable analyses were adjusted for: age at baseline (continuous, in years), tobacco smoking status (coded as never, former, current smoker), number of cigarettes smoked per day, and years of smoking (both continuous, centered)), body height (continuous, m), BMI (<18.5, 18.5-<25, 25-<30, ≥30 kg/m2), non-occupational physical activity (<30, 30-60, 61-90, ≥90 min/day), history of selected diseases at baseline (physician-diagnosed myocardial infarction, angina pectoris, stroke, cancer (excluding skin cancer), diabetes and hypertension; categorized as 0,1,2,3+ diseases), highest level of education (primary school or lower vocational, secondary or medium vocational, and higher vocational or university), alcohol intake (continuous, glasses/week), energy intake (continuous, kcal/day).

Table 7. Multivariable-adjusted[a] RRs for reaching longevity according to alcohol intake in men and women, by strata of smoking and other factors, NLCS.

	Alcohol intake (g/day)							
	Abstainers	>0-<5	5-<15	15-<30	30+	P for trend	Continuous, per 10 g/d	P for interaction
Overall								
90+ / N	345/1391	507/1710	312/1117	166/742	86/447		1416/5407	
RR	1 (Ref.)	1.19	1.36	1.30	1.32	0.009	1.05	
(95 %CI)		(1.07 - 1.34)	(1.20 - 1.55)	(1.10 - 1.53)	(1.06 - 1.64)		(1.01 - 1.09)	
Smoking status								
Never smokers								
90+ / N	276/908	336/899	134/324	48/115	8/28		802/2274	
RR	1 (Ref.)	1.19	1.31	1.31	0.98	0.053	1.06	0.662
(95 %CI)		(1.05 - 1.35)	(1.11 - 1.55)	(1.03 - 1.66)	(0.56 - 1.71)		(0.99 - 1.15)	
Former smokers								
90+ / N	48/260	112/467	119/476	66/338	45/207		390/1748	
RR	1 (Ref.)	1.21	1.43	1.18	1.31	0.450	1.02	
(95 %CI)		(0.90 - 1.63)	(1.06 - 1.91)	(0.85 - 1.64)	(0.91 - 1.87)		(0.95 - 1.08)	
Current smokers								

90+ / N	21/223	59/344	59/317	52/289	33/212		224/1385	
RR	1 (Ref.)	1.56	1.88	2.04	1.87	0.040	1.08	
(95 %CI)		(0.99 - 2.47)	(1.19 - 2.98)	(1.28 - 3.25)	(1.10 - 3.18)		(1.01 - 1.16)	
BMI (kg/m2)								
18.5-<25								
90+ / N	199/734	269/912	184/613	99/394	57/240		808/2893	
RR	1 (Ref.)	1.11	1.36	1.33	1.50	<0.001	1.08	0.110
(95 %CI)		(0.95 - 1.29)	(1.15 - 1.61)	(1.08 - 1.63)	(1.15 - 1.96)		(1.03 - 1.14)	
25+								
90+ / N	142/634	233/779	126/495	66/341	29/202		596/2451	
RR	1 (Ref.)	1.35	1.42	1.32	1.10	0.793	1.00	
(95 %CI)		(1.14 - 1.61)	(1.15 - 1.76)	(1.01 - 1.72)	(0.75 - 1.59)		(0.94 - 1.07)	
Physical activity (min/day)								
=<30								
90+ / N	122/476	129/481	65/263	33/184	16/116		365/1520	
RR	1 (Ref.)	1.06	1.19	1.05	1.02	0.847	1.00	0.256
(95 %CI)		(0.87 - 1.31)	(0.92 - 1.55)	(0.73 - 1.50)	(0.61 - 1.70)		(0.92 - 1.10)	
>30								
90+ / N	223/915	378/1229	247/854	133/558	70/331		1051/3887	
RR	1 (Ref.)	1.29	1.47	1.44	1.48	0.002	1.06	
(95 %CI)		(1.13 - 1.48)	(1.26 - 1.72)	(1.20 - 1.74)	(1.16 - 1.88)		(1.02 - 1.11)	
Level of education								
Primary school, lower vocational								
90+ / N	216/890	277/960	143/506	52/324	24/143		712/2823	
RR	1 (Ref.)	1.20	1.52	1.08	1.18	0.357	1.02	0.172
(95 %CI)		(1.04 - 1.40)	(1.27 - 1.82)	(0.82 - 1.43)	(0.79 - 1.76)		(0.95 - 1.10)	
Secondary, medium vocational								

90+ / N	103/395	174/581	121/437	77/293	34/187		509/1893	
RR	1 (Ref.)	1.14	1.29	1.45	1.27	0.025	1.08	
(95 %CI)		(0.93 - 1.38)	(1.04 - 1.60)	(1.13 - 1.85)	(0.91 - 1.78)		(1.02 - 1.14)	
Higher vocational, university								
90+ / N	26/106	56/169	48/174	37/125	28/117		195/691	
RR	1 (Ref.)	1.48	1.33	1.68	1.68	0.110	1.04	
(95 %CI)		(1.00 - 2.20)	(0.88 - 2.01)	(1.08 - 2.63)	(1.01 - 2.78)		(0.96 - 1.13)	
History of selected disease at baseline								
No								
90+ / N	205/677	334/939	206/618	106/418	63/270		914/2922	
RR	1 (Ref.)	1.24	1.38	1.23	1.38	0.056	1.03	0.534
(95 %CI)		(1.08 - 1.42)	(1.18 - 1.61)	(1.01 - 1.50)	(1.07 - 1.78)		(0.99 - 1.09)	
Yes								
90+ / N	140/714	173/771	106/499	60/324	23/177		502/2485	
RR	1 (Ref.)	1.15	1.41	1.55	1.23	0.032	1.09	
(95 %CI)		(0.95 - 1.40)	(1.12 - 1.77)	(1.17 - 2.06)	(0.81 - 1.87)		(1.01 - 1.17)	

[a] Multivariable analyses were adjusted for: age at baseline (continuous, in years), sex, tobacco smoking status (coded as never, former, current smoker), number of cigarettes smoked per day, and years of smoking (both continuous, centered)), body height (continuous, m), BMI (<18.5, 18.5-<25, 25-<30, ≥30 kg/m2), non-occupational physical activity (<30, 30-60, 61-90, ≥90 min/day), history of selected diseases at baseline (physician-diagnosed myocardial infarction, angina pectoris, stroke, cancer (excluding skin cancer), diabetes and hypertension; categorized as 0,1,2,3+ diseases), highest level of education (primary school or lower vocational, secondary or medium vocational, and higher vocational or university), energy intake (continuous, kcal/day).

There was no significant association with pattern of drinking (Table 6). Although binge drinkers seemed to have a lower probability of reaching 90 than non-binge drinkers, especially in women, the multivariable-adjusted associations were non-significant. This may be due to the small proportion of binge drinking women. When binge drinking was further categorized according to frequency, lower chances of longevity were found in more frequently binge drinking men, but the trend test was not significant.

In subgroup analyses of alcohol and longevity, categorical (or continuous) alcohol intake showed no significant interactions with smoking status, BMI, physical activity, level of education, or history of diseases at baseline (Table 7). Significant associations between alcohol and probability of reaching 90 were seen in many subgroups, including never and current smokers, and those with or without a history of selected diseases. The highest RRs were generally observed in those drinking 5-<15 g/day.

Discussion

In this large prospective study, we found statistically significant positive associations between alcohol intake and the probability of reaching 90 years in both men and women. Overall, the highest probability was found in those consuming 5-<15 g/d alcohol, which corresponds to 0.5-1.5 glass of alcoholic beverage per day. The exposure-response relationship was significantly nonlinear in women, but not in men. Whereas the probability of longevity was decreasing in women with alcohol intakes above 15 g/d, it remained elevated at higher alcohol consumption levels in men. In beverage-specific analyses, wine intake was positively associated with longevity (notably in women), whereas liquor was positively associated with longevity in men and inversely in women. Binge drinking was not significantly associated with longevity, but the risk estimates indicate to avoid binge drinking. In subgroup analyses, alcohol intake was associated with longevity in those with or without a history of selected diseases.

Previous prospective studies on longevity from the US and France that reported on alcohol were rather limited (no alcohol focus) and found no significant associations using longevity cut-offs of 75 (12) and 90 years (13, 25). However, higher alcohol intakes were seen in survivors compared to non-survivors (25), and in subsequent analyses (85+ years) of the Framingham Heart Study(26). The Physicians Health Study among US male physicians (survival cut-off 90) reported small, and non-significantly increased chances of longevity for various drinking categories compared to rarely/never alcohol drinkers, with no dose-response relationship (13). The association between alcohol drinking and longevity was studied twice in the Honolulu Heart Program (HHP) among Japanese-American men using 85 years as longevity cut-off (10, 11). Heavy alcohol intake, measured at baseline age 45-68 years, was significantly inversely related to longevity (OR=0.63, for 3+ drinks/day versus drinking less) (10). In the second analysis, moderate-heavy alcohol intake around 75 years was also significantly inversely related to longevity (OR=0.66, for drinking >14.5 g/day versus less) (11). The fact that the HHP-study was conducted

among men of Japanese ancestry may (partly) explain the more negative association of alcohol with longevity, and suggests a potential mechanism. It is known that east Asians are less efficient alcohol metabolizers due to a common loss-of-function variant of the ALDH2-gene which decreases breakdown of acetaldehyde, the first, toxic alcohol metabolite (27). It could be that those who nevertheless drink experience a higher mortality risk.

Overall, the results of previous longevity studies seem quite limited. Our detailed analyses show significantly positive associations between alcohol and longevity in both men and women, which is in agreement with the PHS (13). Overall in men and women combined in the NLCS, the highest probability of reaching 90 was found in those consuming 5-<15 g/d alcohol, with a HR of 1.36 compared to abstainers. Women experience higher blood alcohol concentrations than men of similar weight due to lower total body water (15). Thus, adverse effects of higher alcohol intakes may appear earlier in women. This might explain the nonlinear exposure-response relationship in women and not in men. We also found that wine intake was positively associated with longevity, whereas liquor was positively associated with longevity in men, and inversely in women. Before speculating on reasons for these beverage differences, future longevity studies are needed to replicate these sex-specific findings, with those on pattern and binge drinking. In mortality studies, there was no clear indication for sex differences (2, 5), and although beneficial associations with wine have been described for mortality, e.g. (2), this topic remains controversial.

As in observational studies on alcohol and mortality (1, 2, 8), studies on alcohol and longevity may be hampered by possible biases (selection and residual confounding biases). Here, selection bias can refer to abstainer bias (when the reference category of non-drinkers also includes sick quitters), the healthy drinker/survivor bias (when cohorts of elderly participants may be overrepresented by healthier drinkers who may have survived adverse effects of alcohol). Reverse causation may occur because health status may influence alcohol drinking (8), which could be addressed by restricting analyses to healthy people at baseline. Incomplete adjustment for confounding factors may lead to residual confounding. In our longevity analysis, we tried to address these possible biases by: 1) excluding ex-drinkers from the reference category; 2) limiting analyses to stable drinkers and abstainers by taking alcohol consumption five years before baseline into account; 3) restricting analyses to participants without prevalent diseases; and 4) adjusting for a large range of possible confounders with detailed information. These analysis strategies do not necessarily provide a full remedy against all possible biases (8), but these were the possibilities with the available data from our cohort. For example, we had no information on lifetime alcohol consumption or consumption on various ages during lifetime, so our analysis of past consumption was limited. After excluding ex-drinkers from the reference category, the analyses in the stable subgroup were essentially similar to what was seen overall. We also found that alcohol intake was associated with longevity in the subgroup without a history of selected diseases. Still, other diseases might have affected alcohol use or longevity.

Residual confounding by socioeconomic status is also possible, because we only controlled for educational level.

It should be noted that the percentages of never drinkers were relatively high in the NLCS: 15% in men and 35% in women, making this common behavior a logical reference category. These percentages were substantially higher than in other cohorts, e.g. 8% in male and 16% in female PLCO-participants (2), and 6% in male and 16% in female EPIC-participants (28). Strengths of the NLCS are the prospective design and high completeness of follow-up, making information bias and selection bias due to differential follow-up unlikely. The validation study of the food frequency questionnaire has shown that it performs relatively well with respect to alcohol (19), but measurement error may still have attenuated associations. The lack of possibilities to update alcohol intake or other lifestyle data during follow-up may have resulted in some attenuated associations too. Our study was aimed at measuring alcohol intake at 68-70 years. Therefore, our study results are limited to alcohol drinking in later life; future longevity studies preferably include lifetime consumption. The alcohol measures in our study were not aimed to get an all-encompassing indication of risky drinking, like in the Alcohol Use Disorders Identification Test/AUDIT (29). Our cutoff for binge drinking (>6 drinks per occasion) as used in the 1980s/1990s (29, 30) is somewhat higher than current cutoffs (29). Because we were interested in the association of late life drinking with longevity, our study likely examined a resilient population that survived already until 68 years despite possible earlier risky drinking.

While older people perceive themselves as controlled responsible drinkers, according to a recent thematic synthesis of qualitative studies, they consider alcohol use often as important part of social occasions, and report that alcohol helps creating feelings of relaxation (31). A possible beneficial effect of light-moderate alcohol intake on longevity (with inverted J-shaped dose-response on longevity) may also be related to hormesis (32, 33). With higher consumption in elderly people, medication may be negatively affected by alcohol, and there is decreased physiological tolerance (34). In conclusion, in this prospective study of men and women aged 68-70 years at baseline, we found the highest probability of reaching 90 years of age for those drinking 5-<15 g alcohol/day. This does not necessarily mean that light-to-moderate drinking improves health. The estimated RR of 1.36 implies a modest absolute increase in this probability and should not be used as motivation to start drinking if one does not drink alcoholic beverages. Although no significant association was found, the risk estimates also indicate to avoid binge drinking.

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Reproductive factors

Chapter 7

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

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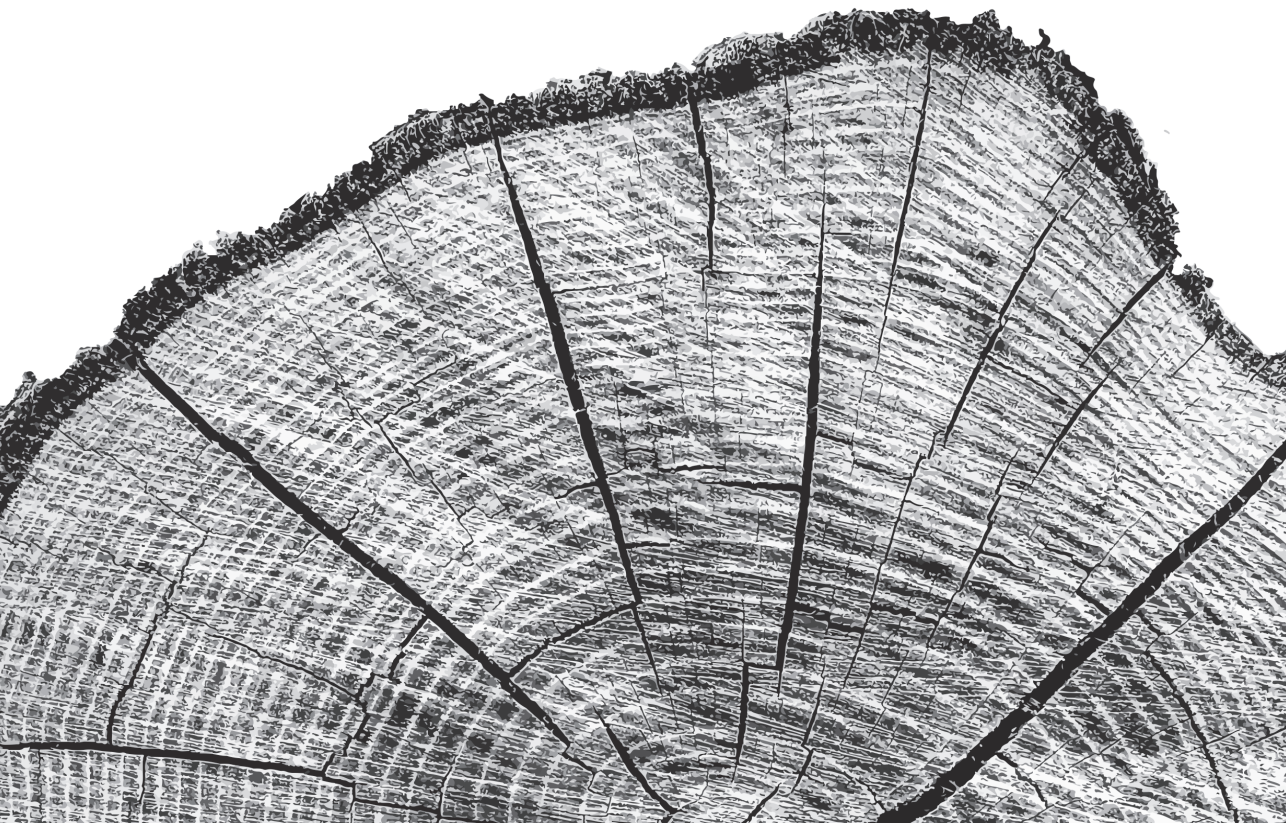
Maturitas. July 2019; 125: 70-80



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

Lloyd Brandts, Frans W.A. van Poppel, Piet A. van den Brandt

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 (longevity).
Study design
For this study, data from the oldest birth cohort (1916-17) of the prospective Netherlands Cohort Study (NLCS) was 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 reaching 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 reaching longevity compared to never HRT-users, but only in women who had an early menopause (<50 years) (RR,1.32; 95% CI, 1.07-1.61).
Conclusion
Age at first childbirth, and ever HRT use in women with an early menopause (<50 years) were associated with the likelihood of reaching the age of 90 years.

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.

Methods

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 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 (Figure 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).

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) usage (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.

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(Figure 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), and 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.

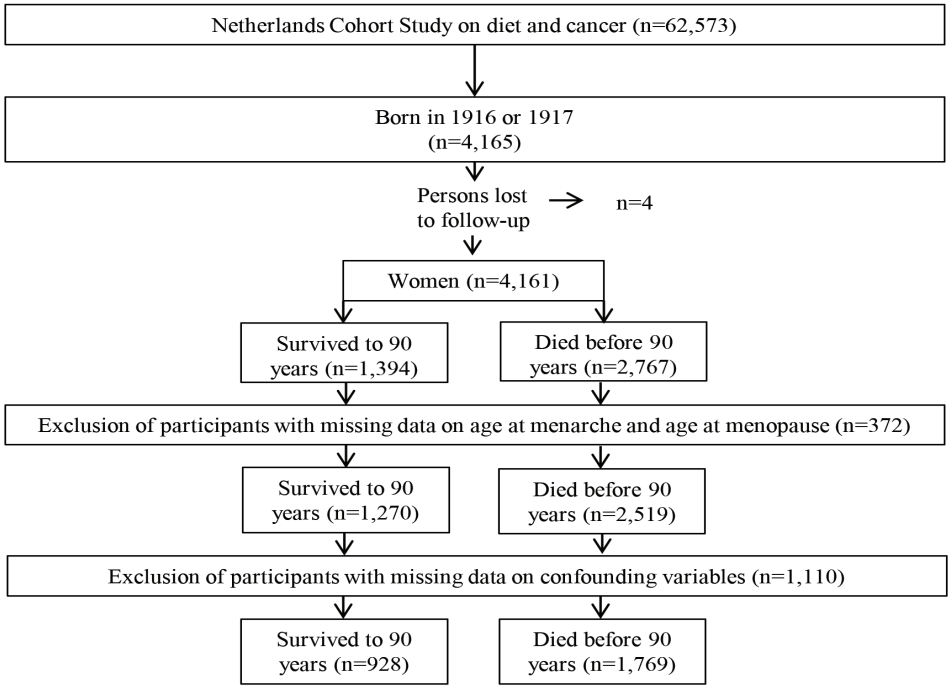


Figure 1: Flow diagram on the analyses between reproductive factors and longevity in a female birth cohort of 1916-17; Netherlands Cohort Study of diet and cancer (1986-2007).

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 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).

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).

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
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.

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 (Figure 2). Menstrual lifespan was not associated with the likelihood of reaching longevity (Table 2).

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).

	median	n	90+	Model 1[a] RR (95% CI)	Model 2[b] 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)
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.

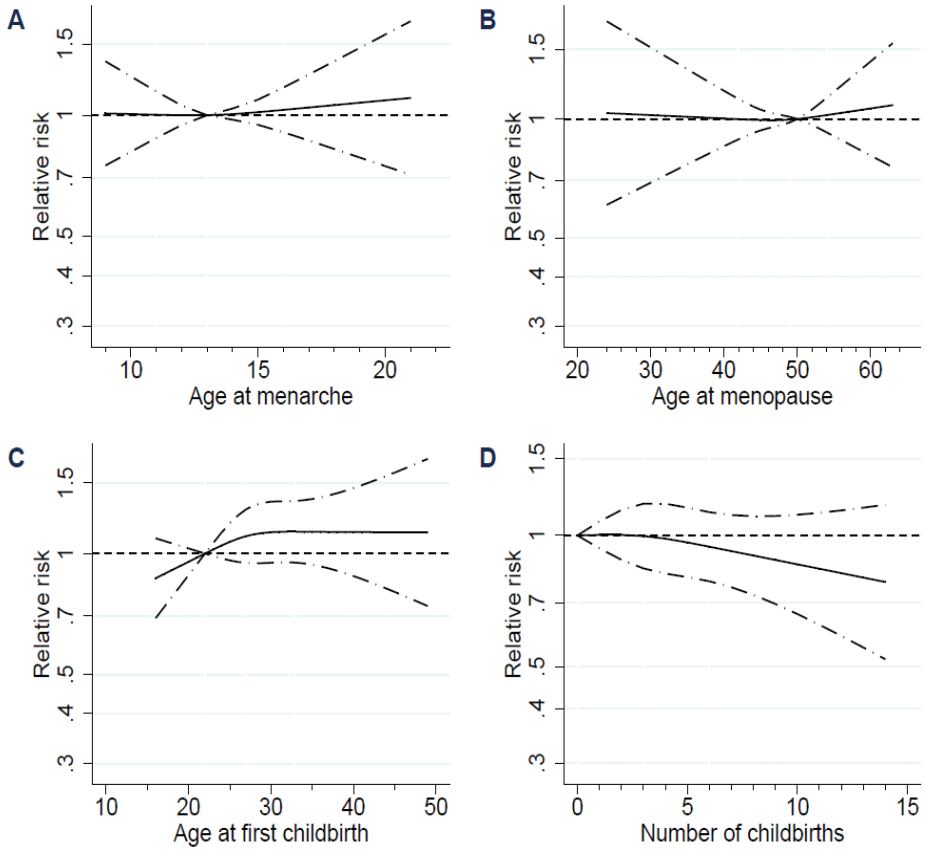


Figure 2: Nonparametric regression curve for the association between age at menarche, age at menopause, and number of childbirths with the likelihood of reaching longevity. Solid line represents point estimate and dashed lines represent 95% confidence intervals. All models were adjusted for age, smoking 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.

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 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, 0.179). No significant interaction by smoking status, and disease history was observed in the relationship between age at menarche and longevity (Table 3). 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).

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								
	Survivors (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								
	Survivors (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								
	Survivors (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								
	Survivors (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				0.301		0.571		0.369
Continuous (per increment of 1 year)								
	Survivors (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								
	Survivors (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								
	Survivors (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								
	Survivors (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								
	Survivors (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				0.004		0.501		0.541
Continuous (per increment of 1 year)								
	Survivors (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.

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).

				Model 1[a]	Model 2[b]
	median	n	80+	RR (95% CI)	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$_{(natural vs. surgical menopause)}$				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)
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				
	Survivors (90+)/n	763/2,260	377/1,161	386/1,099
	RR (95% CI)[a]	Reference	Reference	Reference
Yes				
	Survivors (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			0.179

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.

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 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, the relationship between age at menarche and longevity was not significantly modified by history of (selected) disease status. However, somewhat stronger, 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 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 the WHI cohort and NLCS cohort is the use of a different statistical method. In the analyses by Shadyab et.al. (2016), 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 twentieth 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 socio-economic background, their own likelihood of reaching an old age might have also been smaller. Unfortunately, information on socio-economic 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 socioeconomic 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 the relationship between age at menopause and longevity was significantly modified by smoking status. 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).

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Psychosocial factors

Chapter 8

Loneliness in later life and reaching longevity: Findings from the Longitudinal Ageing Study Amsterdam (LASA)

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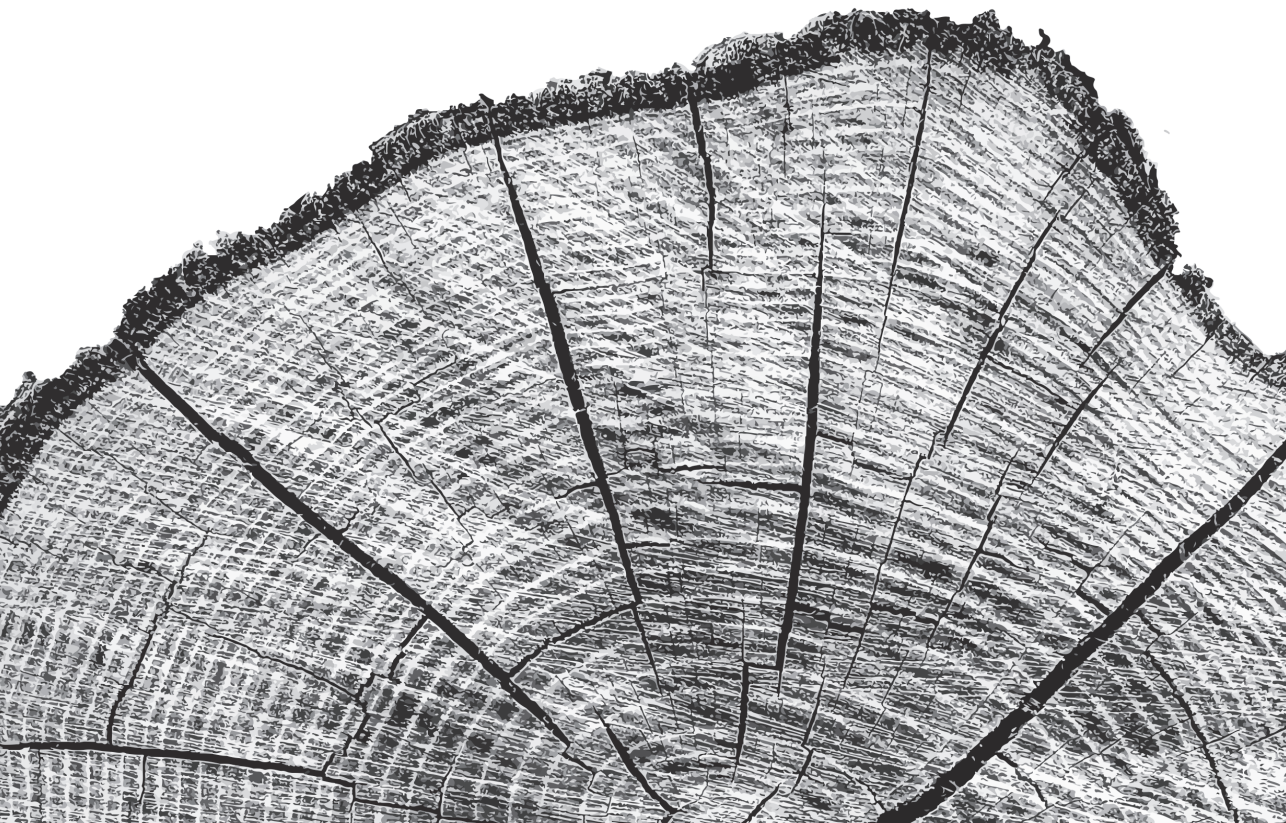
Submitted for publication



Loneliness in later life and reaching longevity: Findings from the Longitudinal Ageing Study Amsterdam (LASA)

Lloyd Brandts, Theo G. van Tilburg, Hans Bosma, Martijn Huisman, Piet A. van den Brandt

Abstract

Introduction

There is an increasing research interest in factors that can characterize those who reach exceptionally old ages. Although loneliness is often associated with an increased risk for premature mortality, its relationship with reaching longevity is still unclear. We aimed to quantify the association between (social/emotional) loneliness and the likelihood of reaching the age of 90 years in both men and women separately.

Methods

For these analyses, data from the Longitudinal Ageing Study Amsterdam (LASA) was used. Loneliness, social loneliness and emotional loneliness were assessed at baseline using the 11-item De Jong-Gierveld scale in 1992-93 (at age 64-85 years). Follow-up for vital status information until the age of 90 years (2018) was 99.5% complete. Multivariable-adjusted Cox regression analyses with a fixed follow-up time were based on 1,032 men and 1,078 women to calculate Risk Ratios (RR) of reaching 90 years.

Results

No significant associations were observed between loneliness and reaching 90 years in both men (RR,0.90; 95%CI,0.70-1.14) and women (RR,0.98; 95%CI,0.83-1.14). Social loneliness was significantly associated with a reduced chance of reaching 90 years in women (RR,0.82; 95%CI,0.67-0.99).

Conclusion

In the current analyses, loneliness was not significantly associated with reaching longevity in both men and women. When investigating specific dimensions of loneliness, we observed that reporting social loneliness was associated with reaching 90 years in women. This indicates that, for women, the size and diversity of a personal network could influence the probability of reaching longevity.

Introduction

With an increasing number of individuals reaching exceptionally old ages, there is an increasing research interest in identifying factors that characterize this group of long-lived individuals. Apart from the added years to life, human longevity has also been associated with delayed morbidity (1). Therefore, identifying factors that are associated with reaching longevity might contribute to the understanding of promoting both longer and healthier lifespans. Human longevity is mostly defined as reaching a specific age that exceeds the life expectancy (2). To date, several studies have identified genetic, and lifestyle-related factors that are associated with an reaching longevity, mostly defined as reaching 90 years (3-9). Few studies investigated the relationship between psychosocial factors and longevity. Recently, two prospective cohort analyses reported a positive association between optimism and social integration, and reaching the age of 85 years (10, 11). While these positive psychosocial traits seem to increase the probability of reaching longevity, it is still unclear whether negative psychosocial treats, such as loneliness, are associated with a decreased probability of reaching longevity.

Loneliness is defined as a perceived lack of social relationships and unfulfilled intimacy (12). Additionally, loneliness can be further distinguished by emotional loneliness, and social loneliness. Emotional loneliness refers to a perceived lack of intimacy or close emotional attachment in relationships, while social loneliness refers perceived lack of a broader group of contacts or engaging in a social network (13).

Loneliness is common among older individuals, and the prevalence seems to increase with age, especially at older ages (75+ years) (14). Based on surveys, it is estimated that around 25 percent of individuals aged 45-79 report moderate or serious loneliness. In individuals aged 80+ years this is estimated to be around 43 percent (15-17). Loneliness has often been linked to an increased chance of premature death. In a meta-analysis on loneliness and mortality, loneliness was associated with all-cause mortality in both men and women (18). Another meta-analysis indicated that the association between loneliness and mortality risk was similar to other well-established risk factors for mortality (19). Berkman et al. (2000) have presented a conceptual model on how (a lack of) social interaction might influence health (20). They describe three downstream pathways through which these psychosocial mechanisms may influence health and longevity namely, via health behavioural-, psychological-, and physiologic pathways (20). In line with this conceptual model, other researchers have suggested that loneliness is associated with a reduced capacity of self-regulation (21), and unhealthy lifestyle habits (22, 23) (23).

During the aging process, the effect that relevant factors might have on the risk of premature mortality might converge or crossover across different stages of life (24). It was also observed that the relationship between loneliness and mortality became weaker with increasing age of the participants (25), which could indicate that long-lived individuals are more resilient to the harmful effects of loneliness. Using data from the Longitudinal Aging Study Amsterdam (LASA) cohort, we aimed to quantify the relationship between loneliness and the likelihood of reaching the age

of 90 years. Because men and women follow different survival patterns (e.g. women have a higher overall probability of reaching 90 years compared to men), all analyses were stratified by sex.

Methods

Study design and population

The Longitudinal Aging Study Amsterdam (LASA) is a prospective cohort study initiated in 1992 to study the physical, emotional, cognitive, and social functioning of individuals aged 55-84 in the Netherlands. In 1992, a sample was recruited from 11 municipal registries within three representative geographic regions in the Netherlands for the Living Arrangements and Social Networks of Older Adults programme (LSN). Participants recruited for this study were born between 1908 and 1937, with an oversampling of older individuals and males. The initial response rate was 62% (n=3,805). From this sample, 3677 surviving participants were contacted for the first LASA cycle (1992-1993) on average 11 months after the LSN interview, with a response rate of 85%. Examinations were performed at the participants' homes, and re-examinations took place about every three years. Detailed information on the data collection procedures have been described elsewhere (26). Mortality follow-up was done by record linkage to the municipal population registries, Basisregistratie Personen (BRP). The last date of mortality follow-up for this study was August 1st, 2018. Because only a part of the full cohort was "at risk" of reaching the age of 90 years at this date, the analyses were restricted to participants born before August 2nd, 1928 (Figure 1). Of these, follow-up for mortality was 99.5% complete. After exclusion of participants with missing data information on loneliness (n=62), 1,032 men and 1,078 women were included for the analyses (Figure 1).

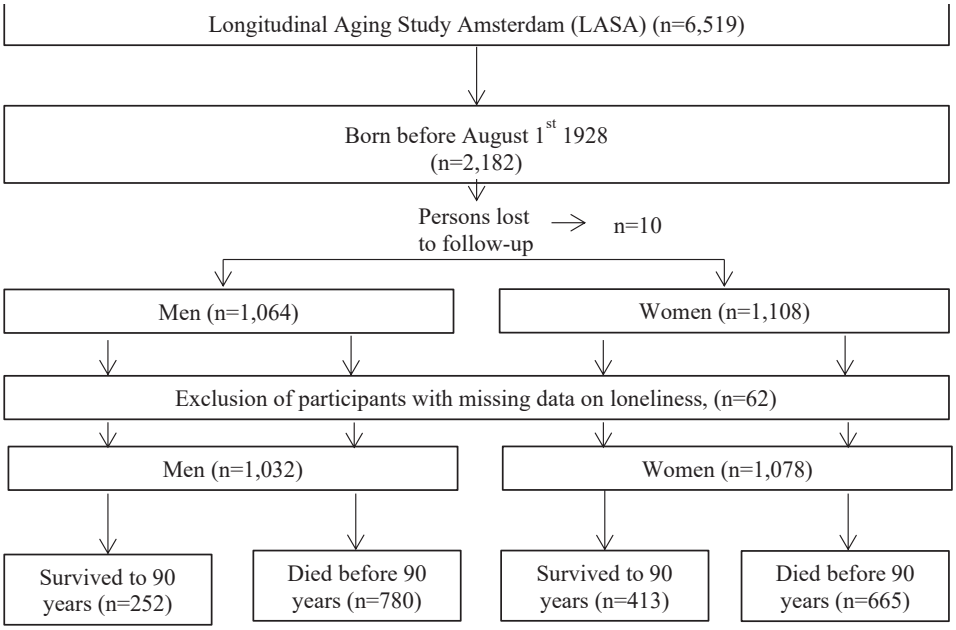


Figure 1: Flow diagram on analyses between loneliness and longevity in an elderly cohort (aged 64-85 years) of the Longitudinal Aging Study Amsterdam (LASA) (1992-2018).

Exposure assessment and outcome

Loneliness has been assessed at baseline by using a validated 11-item De Jong-Gierveld scale (27) in 1992-93. Items scores have been computed into an overall measure of loneliness ranging from 0 (no loneliness) to 11 (severe loneliness). Loneliness was also computed into a dichotomous variable, in which a participant is considered mildly or severely lonely at a cut-off score of ≥3 on the loneliness scale, as has been done in other studies before (28).

Two dimension of loneliness can be further distinguished from the overall loneliness scale items, namely emotional loneliness (ranging 0-6) and social loneliness (range 0-5). Participants who scored ≥2 out of six emotional loneliness items were considered emotionally lonely. Those scoring ≥2 out of five social loneliness items were considered socially lonely (28). Reaching the age of 90 years (yes/no) was used as outcome measure.

Statistical Analyses

Baseline characteristics were presented with mean values for continuous variables and with percentages for categorical variables. Characteristics were presented by survival status at age 90 years and experienced loneliness at baseline, both stratified by sex. The association between loneliness and the likelihood of reaching 90 years was assessed using age- and multivariable-adjusted Cox regression models with a fixed follow-up time (29, 30). Huber-White sandwich estimator were used to calculate standard errors to account for underdispersion (31). For the multivariable-

adjusted analyses, a priori confounders were selected based on literature and directed acyclic graphs (DAGs). Baseline age (years, continuous), educational level (primary/lower vocational, junior/senior high school, higher vocational/university), and marital status (never married, married, divorced, widowhood) were selected as confounders for our main analyses. Additional adjustments were made for number of (selected) chronic diseases at baseline (0,1,2, 3 or more from non-specific lung diseases (CNSLD), cardiac diseases, peripheral artery disease (PAD), diabetes mellitus, stroke, arthritis, and malignancies) and the Mini Mental State Examination (MMSE) score (0-30, continuous) in model 3, and smoking status (never, former, current, and missing), Body Mass Index (BMI) (<18.5, 18.5-<25, 25-<30, 30+ kg/m2, and missing), total minutes of non-occupational physical activity per day(<30, 30-<60, 60-<90, 90-<120, ≥120, and missing) and number of alcohol beverages per week (0, >0-<1, 1-<5, 5-<10, 10+, and missing) in model 4. Although we consider these additional variables as potential confounders, these factors might also act as a mediator, making it more difficult to interpret the additionally-adjusted results. All analyses were stratified by sex.
After evaluation of the confounding variables, we observed missing values (n=548) on confounding lifestyle factors including smoking status, BMI, physical activity, alcohol intake, educational level, and MMSE (Table 1 & 2). To limit bias that might occur due to this dropout, a multiple imputation approach with twenty iterations was performed, based on linear (for continuous variables), and logistic (for categorical variables) regression models. Information on loneliness, marital status, number of selected disease, smoking status, BMI, non-occupational physical activity, alcohol consumption, education level and reaching the age of 90 (yes/no) were used as predictors for the imputed data.

Results

In this study, the average probability (age-standardized) of reaching the age of 90 years was 0.25 in men, and 0.38 in women (Table 1). Having a higher vocational or university degree, and reporting no (selected) diseases at baseline was more common in those who survived to 90 years, compared to those who died before this age (Table 1).
Regarding lifestyle factors, men who survived to 90 years were less often current smokers (19.4% vs. 30.0%), were less often obese (≥30 kg/m2; 7.5% vs. 8.9%), had a somewhat higher average level of physical activity (150 min/day vs. 131 min/day), and drank less alcoholic beverages per week (8.3 vs 9.2 drinks/wk). Women who survived to 90 years were also less often current smokers (7.3% vs. 14.3%), but drank more alcoholic beverages per week (4.1 vs 3.5 drinks/wk). However, it has to be noted that both men and women who died before 90 years were more likely to have missing information on lifestyle characteristics, compared to those who survived to 90 years (Table 1).

In Table 2, we observed that both men and women who experienced loneliness, were less often married, and had more often at least one (selected) chronic disease at baseline. Those who experienced loneliness were also more likely to have missing information on lifestyle characteristics (Table 2).

Table 1: Baseline characteristics of the cohort members overall and by survival status in an elderly cohort (aged 64-85 years) of the Longitudinal Aging Study Amsterdam (LASA) (1992-2018).

	Men			Women		
	Total	Survived to 90 years	Died before age 90 years	Total	Survived to 90 years	Died before age 90 years
N, (%)[a]	1,032	252 (24.4)	780 (75.6)	1,078	413 (38.3)	665 (61.7)
Age at baseline, Mean ± SD	75.4 ± 5.9	76.2 ± 6.2	75.1 ± 5.8	75.2 ± 6.1	76.0 ± 6.3	74.6 ± 5.9
Age-standardized survival to 90 years, %		24.8			38.2	
Loneliness scale (0-11), Mean ± SD	2.1 ± 2.5	2.1 ± 2.4	2.2 ± 2.5	2.5 ± 2.8	2.4 ± 2.7	2.5 ± 2.8
Loneliness (≥3 pt), (%)	32.6	31.8	32.8	37.9	38.0	37.7
Emotional loneliness scale (0-6), Mean ± SD	1.1 ± 1.6	1.0 ± 1.5	1.1 ± 1.6	1.5 ± 1.9	1.5 ± 1.9	1.5 ± 1.9
Emotional loneliness (≥2 pt), (%)	26.3	25.0	26.7	38.3	36.8	39.3
Social loneliness scale (0-5), Mean ± SD	1.1 ± 1.4	1.1 ± 1.4	1.1 ± 1.4	0.9 ± 1.4	0.9 ± 1.3	1.0 ± 1.4
Social loneliness (≥2 pt), (%)	28.0	27.4	28.2	23.3	20.3	25.1
Educational level, (%)						
Primary/ lower vocational	61.4	57.1	62.8	74.0	68.8	77.3
Junior/ senior high school	25.2	27.0	24.6	19.1	23.0	16.7
Higher vocational/ University	13.4	15.9	12.6	6.9	8.2	6.0
Marital Status, (%)						
Never married	4.6	5.2	4.4	6.9	7.3	6.6
Married	75.1	73.0	75.8	42.3	39.0	44.4
Divorced	4.2	5.6	3.7	5.1	5.8	4.7
Widowhood	16.2	16.3	16.2	45.7	47.9	44.4
Number of (selected) diseases at baseline, (%)						

0	36.3	46.4	33.1	30.0	34.4	27.2
1	35.3	36.1	35.0	36.9	37.3	36.7
2	18.8	12.7	20.8	21.8	21.3	22.1
3 or more	9.6	4.8	11.2	11.3	7.0	14.0
Mini Mental State Examination score (0-30), Mean ± SD	26.5 ± 3.2	27.1 ± 2.6	26.4 ± 3.3	26.4 ± 3.3	26.9 ± 2.6	26.1 ± 3.6
Smoking status, (%)						
Never	5.9	9.1	4.9	48.9	54.7	45.3
Former	53.4	61.5	50.8	23.0	24.2	22.3
Current	27.4	19.4	30.0	11.6	7.3	14.3
Missing	13.3	9.9	14.3	16.5	13.8	18.2
Body Mass index (kg/m^2)[b], Mean ± SD	25.8 ± 3.3	25.8 ± 3.1	25.9 ± 3.3	27.8 ± 4.7	27.7 ± 4.5	27.9 ± 4.8
Body Mass index (kg/m^2), (%)						
<18.5 kg/m^2	0.9	0.4	1.0	1.0	0.2	1.5
18.5-<25 kg/m^2	33.6	36.1	32.8	21.7	23.5	20.6
25-<30 kg/m^2	41.3	44.8	40.1	33.5	36.8	31.4
≥30 kg/m^2	8.5	7.5	8.9	23.6	22.3	24.4
Missing	15.7	11.1	17.2	20.2	17.2	22.1
Total physical activity (min/day)[b], Mean ± SD	136 ± 106	150 ± 110	131 ± 105	176 ± 106	179 ± 106	174 ± 106
Total physical activity (min/day), (%)						
<30 min/day	10.9	6.8	12.2	5.0	2.9	6.3
30-<60 min/day	10.5	8.7	11.0	5.0	5.1	5.0
60-<90 min/day	12.9	15.9	11.9	8.0	8.0	8.0
90-<120 min/day	14.4	13.9	14.6	8.9	10.4	8.0
120+ min/day	44.3	48.0	43.1	64.5	67.3	62.7
Missing	7.1	6.8	7.2	8.6	6.3	10.1
Number of alcoholic beverages per week[b], Mean ± SD	9.0 ± 10.4	8.3 ± 8.6	9.2 ± 10.9	3.7 ± 6.5	4.1 ± 6.4	3.5 ± 6.5

Number of alcoholic beverages per week, (%)						
0 (Abstainers)	15.9	13.9	16.5	26.4	23.5	28.2
>0-<1 drink per week	7.1	6.8	7.2	13.5	13.6	13.5
1-<5 drinks per week	15.7	17.5	15.1	21.8	24.5	20.2
5-<10 drinks per week	19.9	23.8	18.6	12.2	12.6	11.9
10+ drinks per week	27.7	27.8	27.7	9.2	11.1	8.0
Missing	13.8	10.3	14.9	16.9	14.8	18.2
Neuroticism (0-50) [c] , Mean ± SD	5.4 ± 5.6	5.0 ± 4.9	5.5 ± 5.9	7.0 ± 6.0	6.8 ± 6.0	7.0 ± 5.9
Mastery (5-25) [c] , Mean ± SD	17.1 ± 3.2	17.5 ± 3.1	17.0 ± 3.3	16.7 ± 3.3	16.8 ± 3.4	16.6 ± 3.2
CES-D score (0-60) [c], Mean ± SD	6.9 ± 6.8	5.9 ± 5.9	7.2 ± 7.0	9.7 ± 8.6	9.2 ± 8.1	10.0 ± 8.9
Depressive symptoms [c] , (%)						
No depressive symptoms	88.8	93.2	87.4	79.7	81.2	78.8
Depressive symptoms	8.0	5.2	8.9	13.3	13.2	13.4
Severe level of depressive symptoms	3.3	1.6	3.8	7.0	5.6	7.8

[a] Number of participants with complete information on loneliness, emotional loneliness, social loneliness, and confounders including: baseline age, educational level, marital status, number of (selected) disease at baseline, and MMSE-score [b] Excluding participants with missing data. [c] Number of participants used may vary from the study population due to missing values on specific exposure variables.

Table 2: Baseline characteristics of the cohort members by sex and loneliness status in an elderly cohort (aged 64-85 years) of the Longitudinal Aging Study Amsterdam (LASA) (1992-2018).

	Men		Women	
	Not lonely	Lonely (≥3pt)	Not lonely	Lonely (≥3pt)
N[a]	696	336	670	408
Age at baseline, Mean ± SD	74.6 ± 5.8	76.9 ± 5.9	74.6 ± 6.2	76.1 ± 5.8
Educational level, n (%)				
Primary/ lower vocational	59.9	64.6	72.2	77.0
Junior/ senior high school	26.6	22.2	19.9	17.9
Higher vocational/ University	13.5	13.2	7.9	5.2
Marital Status, n (%)				
Never married	2.6	8.6	6.7	7.1
Married	84.3	56.0	51.0	27.9
Divorced	3.2	6.3	4.6	5.9
Widowhood	9.9	29.2	37.6	59.1
Number of (selected) diseases at baseline, n (%)				
0	38.1	32.7	32.8	25.3
1	35.2	35.4	38.5	34.3
2	17.0	22.6	19.1	26.2
3 or more	9.8	9.2	9.6	14.2
Mini Mental State Examination score (0-30), Mean ± SD	26.8 ± 2.7	25.9± 4.0	26.7 ± 3.0	25.9 ± 3.7
Smoking status, (%)				
Never	6.5	4.8	50.1	45.8
Former	55.5	49.1	23.1	22.8
Current	25.6	31.3	10.9	12.8
Missing	12.5	14.9	15.2	18.6
Body Mass index (kg/m^2)[b], Mean ± SD	25.9 ± 3.1	25.7 (3.6)	28.0 ± 4.5	27.5 (5.1)
Body Mass index (kg/m^2), (%)				
<18.5 kg/m^2	0.6	1.5	0.6	1.7
18.5-<25 kg/m^2	34.2	32.4	20.0	24.5
25-<30 kg/m^2	42.1	39.6	37.0	27.7
≥30 kg/m^2	8.5	8.6	24.5	22.1
Missing	14.7	17.9	17.9	24.0
Total physical activity (min/day)[b], Mean ± SD	137 ± 105	134 ± 110	186 ± 107	159 ± 103

Total physical activity (min/day), (%)				
<30 min/day	9.3	14.0	3.0	8.3
30-<60 min/day	10.5	10.4	4.5	5.9
60-<90 min/day	13.8	11.0	8.2	7.6
90-<120 min/day	16.2	10.7	8.4	9.8
120+ min/day	44.8	43.2	68.4	58.1
Missing	5.3	10.7	7.6	10.3
Number of alcoholic beverages per week[b], Mean ± SD	8.8 ± 9.9	9.3 ± 11.3	3.8 ± 6.6	3.6 ± 6.3
Number of alcoholic beverages per week, (%)				
0 (Abstainers)	15.1	17.6	27.2	25.3
>0-<1 drink per week	7.3	6.6	12.2	15.7
1-<5 drinks per week	15.0	17.3	22.5	20.6
5-<10 drinks per week	21.6	16.4	13.1	10.5
10+ drinks per week	28.0	27.1	9.3	9.1
Missing	13.1	15.2	15.7	18.9
Neuroticism (0-50)[c], Mean ± SD	4.4 ± 4.7	7.6 ± 6.9	5.6 ± 5.2	9.7 ± 6.5
Mastery (5-25)[c], Mean ± SD	17.7 ± 3.0	15.9 ± 3.4	17.4 ± 3.0	15.4 ± 3.4
CES-D score (0-60) [c], Mean ± SD	5.0 ± 4.9	10.8 ± 8.3	6.9 ± 6.1	14.4 ± 10.0
Depressive symptoms[c], (%)				
No depressive symptoms	95.9	73.6	90.5	61.7
Depressive symptoms	3.6	17.2	7.2	23.4
Severe level of depressive symptoms	0.4	9.2	2.3	14.9

[a] Number of participants with complete information on loneliness, emotional loneliness, social loneliness, baseline age, educational level, marital status, number of (selected) disease at baseline, and MMSE-score.[b] Excluding participants with missing data. [c] Number of participants used may vary from the study population due to missing values on specific exposure variables.

In both men and women, no significant associations were observed between loneliness and reaching longevity in dichotomous and continuous analyses (Table 3). However, the main analyses (model 2) pointed towards a non-significant association between loneliness (yes vs. no) and reaching 90 years in men (RR,0.90; 95%CI, 0.70-1.14), and in women (RR,0.98; 95%CI,0.83-1.15). The disease-, and lifestyle-adjusted analyses (model 4) pointed towards a 10% non-significant increased probability in exposed women, compared to non-exposed women (RR, 1.10; 95%CI, 0.94-1.28).

Point estimates of effect suggested that emotional loneliness was non-significantly inversely associated with reaching 90 years in both men (RR,0.86; 95%CI,0.65-1.12), and women (RR,0.90; 95%CI,0.76-1.05) in the main analyses. After additional confounder adjustment, the effect estimates attenuated. In the main analyses, social loneliness was significantly inversely associated with reaching 90 years in women (RR,0.82; 95%CI,0.67-0.99), and non-significantly inverse in men (RR,0.93; 95%CI,0.73-1.18). Additional adjustment for disease and lifestyle factors attenuated the effect estimates to RR,0.92; 95%CI,0.76-1.12 in women, and RR,1.02; 95%CI,0.80-1.30 in men (Table 3).

Table 3: Age- and multivariable-adjusted Cox regression models with a fixed follow-up time between loneliness, emotional loneliness and social loneliness, and the likelihood of reaching 90 years in an elderly cohort (aged 64-85 years) of the Longitudinal Aging Study Amsterdam (LASA) (1992-2018).

	Males				Females			
	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Loneliness (0-11)								
Dichotomous								
No (<3 pt)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Yes (≥3 pt)	0.91 (0.72-1.15)	0.90 (0.70-1.14)	0.94 (0.74-1.20)	0.97 (0.77-1.24)	0.98 (0.83-1.14)	0.98 (0.83-1.15)	1.04 (0.88-1.21)	1.10 (0.94-1.28)
Continuous (per 1pt increment)	0.98 (0.94-1.02)	0.98 (0.93-1.02)	0.99 (0.95-1.04)	1.00 (0.96-1.05)	0.99 (0.96-1.01)	0.98 (0.96-1.01)	1.00 (0.97-1.03)	1.01 (0.98-1.04)
Emotional loneliness (0-6)								
Dichotomous								
No (<2pt)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Yes (≥2 pt)	0.87 (0.68-1.11)	0.86 (0.65-1.12)	0.92 (0.71-1.20)	0.95 (0.73-1.23)	0.91 (0.77-1.06)	0.90 (0.76-1.05)	0.97 (0.82-1.14)	1.01 (0.86-1.18)
Continuous (per 1pt increment)	0.96 (0.90-1.03)	0.96 (0.89-1.03)	0.98 (0.91-1.06)	1.00 (0.92-1.07)	0.99 (0.95-1.03)	1.00 (0.96-1.04)	1.01 (0.97-1.05)	1.03 (0.99-1.07)
Social loneliness (0-5)								
Dichotomous								
No (<2pt)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Yes (≥2 pt)	0.94 (0.74-1.20)	0.93 (0.73-1.18)	0.96 (0.75-1.22)	1.02 (0.80-1.30)	0.82 (0.68-1.00)	0.82 (0.67-0.99)	0.84 (0.70-1.02)	0.92 (0.76-1.12)
Continuous (per 1pt increment)	0.99 (0.92-1.06)	0.98 (0.91-1.06)	0.99 (0.92-1.07)	1.01 (0.94-1.09)	0.96 (0.90-1.01)	0.95 (0.90-1.01)	0.97 (0.91-1.03)	0.99 (0.94-1.05)

[a] Age-adjusted model. [b] **Main model** adjusted for baseline age, educational level (primary/ lower vocational, junior/ senior high school, higher vocational/ university), and marital status (never married, married, divorced, widowhood). [c] Additionally adjusted for number of (selected) diseases at baseline (0, 1, 2, 3 or more), and MMSE-score (0-30; continuous). [d] Additionally adjusted for smoking status (never, former, current), Body mass index (<18.5, 18.5-<25, 25-<30 30+ kg/m2), total physical activity per day (<30, 30-<60, 60-<90, 90-<120, 120 min/day), number of alcoholic beverages per week (0, >0-<1, 1-<5, 5-<10, 10+ drinks/wk).

Discussion

Based on data from the LASA cohort, we observed that loneliness was not significantly associated with reaching the age of 90 years in both men and women. When we distinguished different dimensions of loneliness, we observed that social loneliness was significantly associated with a reduced chance of reaching the age of 90 years in women.

In the current analyses, no significant associations were observed between loneliness and reaching longevity. Although the literature on loneliness and longevity is scarce, several studies studied the relationship between loneliness and premature mortality. In a meta-analyses of 35 articles investigating the relationship between loneliness and all-cause mortality, a pooled HR of 1.44 (95%CI, 1.19-1.76) in men and a pooled HR of 1.26 (95%CI, 1.10-1.35) in women was observed (18). Furthermore, loneliness was also significantly associated with an increased mortality risk in an earlier analysis of the LASA cohort (32). However, this analysis on mortality also included participants who were younger at baseline (aged 55-63 years). It is known that feelings of loneliness increase during aging due to the decline in social contacts, and are even common among the very old (14, 16). Because of the inherent decline of social contacts at older ages, loneliness could be experienced as a natural consequence of aging. In contrast, younger individuals who experience loneliness might experience that their situation is culturally divergent, which could pose an additional threat to their self-esteem and mental well-being (19). This could indicate that the effect of loneliness on mortality differs throughout the life course, and might explain why the results of our study, differed from the results observed in the earlier analyses within the LASA cohort (32). However, this hypothesis remains speculative and should be tested. Furthermore, replication of our findings in other cohorts is needed. One meta-analysis did report that the effect estimates between loneliness and mortality became weaker with increasing ages of the participants (25), which might partially explain the weaker effect estimates observed in the current study. Alternatively, the current analyses might illustrate that the etiology of premature mortality is not necessarily similar to the etiology of reaching exceptionally high ages, or longevity.

Although no significant association was observed between loneliness and longevity, we did find a significant association between social loneliness and a decreased chance of reaching 90 years in women. An individual might experience social loneliness when there is an absence of a broader group of contacts or engaging in a social network (13). In previous studies, it has been observed that a larger size and diversity of the social network were more strongly associated with a reduced risk for mortality in older individuals, compared to functional characteristics like emotional support (34, 35). Furthermore, there is evidence that, with aging, men are focusing more on emotionally rewarding relationships, while women seem to have larger instrumental networks (36, 37). This could indicate that, at least for women, the size and diversity of a personal network might be more important for reaching longevity than having an intimate relationship at an older age. However, additional adjustment for number of selected diseases at baseline and other lifestyle factors did attenuate the results. Therefore, the exact mechanism on how social and emotional loneliness are associated with reaching longevity in both sexes needs to be further explored and replicated in other longitudinal cohort studies as well.

As in studies on mortality, the causal direction between loneliness, and unfavorable lifestyle characteristics and disease occurrence remains questionable. In the current

study, adjustments were made for history of chronic diseases at baseline, and lifestyle characteristics. In these analyses, the effect estimates between (the different dimensions of) loneliness became weaker, which might indicate that these factors partially explain the unfavorable association between loneliness and longevity. However, because adjustment for mediating factors might introduce bias, we consider the effect estimates with adjustment for pre-exposure covariates (e.g. marital status and educational level) less biased than the fully adjusted effect estimates.

The strengths of this study are the large sample size, and the long and complete follow-up for mortality (99.5%). The prospective study design limits the risk for information bias and selection bias due to differential follow-up. Furthermore, loneliness was assessed using a reliable and valid measurement instrument (27). A limitation that should be considered is that loneliness the confounding factors was only based on observation at baseline (in 1992-93). Furthermore, residual confounding by baseline age might have influenced our results. It is known that individuals report more loneliness with increasing age. The ages at which the participants were included in the study was broad (ages 64-85). While older individuals are more likely to report loneliness, they also have a higher (conditional) chance of reaching 90 years of age at baseline, which might have led to an underestimation of the association between loneliness and longevity. We did account for this potential confounding effect by adjusting for baseline age in the multivariable-adjusted models. Despite this measure, we should not rule out the possibility of residual confounding by baseline age. Therefore, we suggest that future studies should prefer stratification by smaller age groups when the sample size allows for that. Furthermore, the participants in this study already survived to older ages, which could have led to survivorship bias. The association between loneliness and longevity might potentially be stronger if younger baseline ages were considered.

In conclusion, we did not observe a significant association between loneliness and longevity in both men and women. Strongest support was observed for an association of social loneliness with longevity in women, which might indicate that in women the quantity of relationships might be more important than the quality of relationship in terms of reaching longevity.

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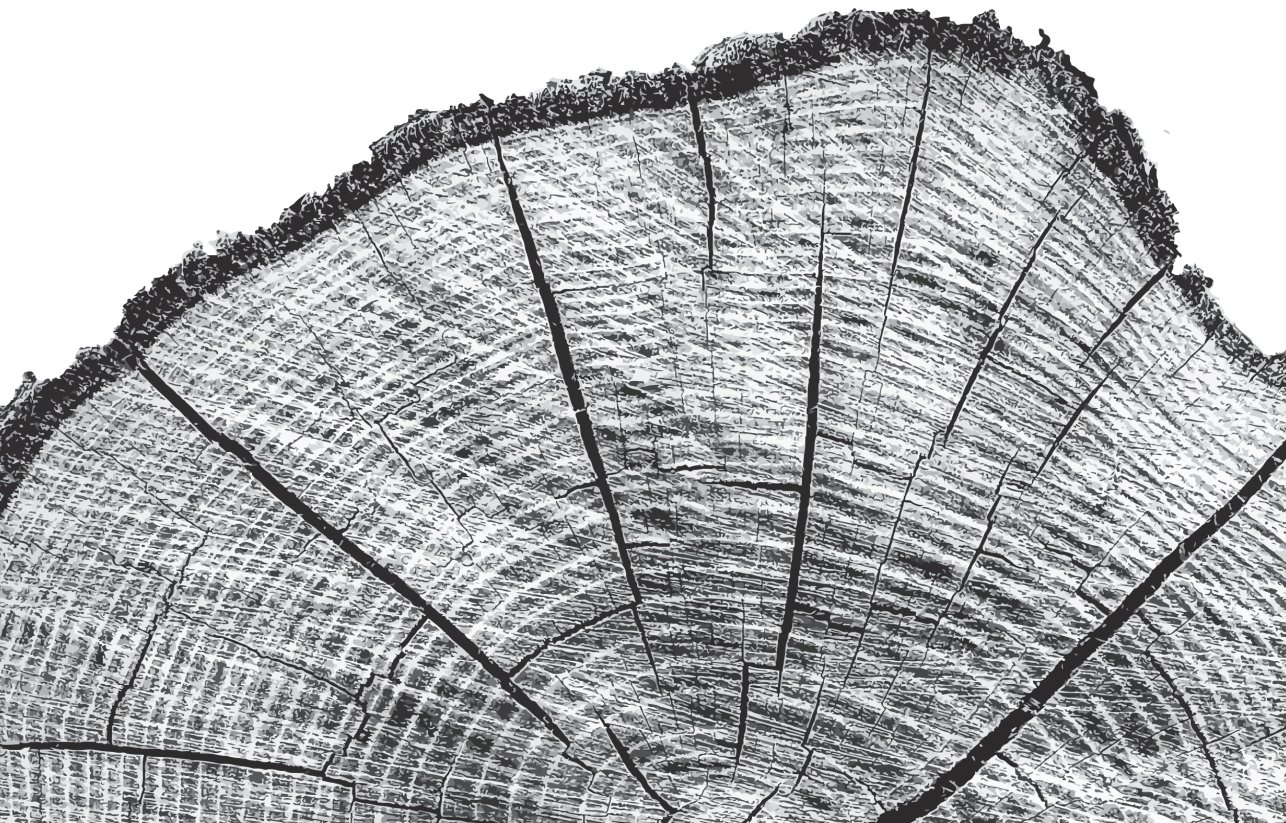
Discussion

Chapter 9
General Discussion



The studies described in this thesis aimed to investigate how several factors relate to the probability of reaching longevity, which we defined as reaching the age of 90 years. In these studies, we have focused on the association with parental lifespan, several lifestyle factors and reproductive factors using detailed questionnaire information from the oldest participants (born 1916-17) of the Netherlands Cohort Study (NLCS). Furthermore, these studies have tried to formulate an answer to several knowledge gaps that we identified in the literature review that we presented in chapter 2. Additionally, we were interested whether psychosocial factors were also associated with reaching an exceptionally high age. Therefore, we tried to assess whether there is a relationship between perceived loneliness and reaching longevity using data from the Longitudinal Aging Study Amsterdam (LASA).

In this chapter, we will provide a brief overview and interpretation of the main findings. Although this dissertation focusses mainly on longevity, in this chapter, we will also shortly reflect on the concept "healthy lifespan", and the maximum lifespan. Lastly, we provide some methodological considerations, and recommendations for future research.

Summary of the main findings

In chapter 2, we observed that smoking, and a low level of physical activity were inversely associated with reaching longevity (1-11). Alcohol intake, and BMI, showed limited and/or contradictory associations with reaching longevity (1, 2, 5, 7, 9, 12). Furthermore, we concluded that parental longevity was significantly associated with reaching longevity, primarily through maternal longevity. Some studies indicated a stronger effect of parental longevity in female offspring compared to male offspring (1, 3, 4). Lastly, we observed a lack of studies investigating the relationship between dietary and reproductive factors, and longevity.

In chapter 3, we observed that both male and female offspring of parents who survived to ages 80 year and older had an increased likelihood of reaching the age of 90 years, compared to those whose parents had died before the age of 80 years. Longevity in parents will most likely not be a direct cause for their offspring to reach longevity. We suggested that this longevity advantage might be passed on to later generations by a combination of early environmental influences and genetic factors. Therefore, we additionally adjusted for some environmental factors that might explain the observed relationship. In these analyses, paternal survival in male offspring and maternal survival in female offspring were still significantly positively associated with an increased likelihood of reaching the age of 90 years. Earlier studies had observed that this association was primarily present for maternal longevity, and not for paternal longevity (3, 4), and more pronounced in female offspring (1, 4, 5).

Regarding lifestyle factors, our analyses have focused on smoking behaviour, body size, levels of non-occupational physical activity, and alcohol intake. In line with the results of chapter 2, our analyses in chapter 4 showed that current and former smokers have a significantly reduced probability of reaching the age of 90 years

compared to never smokers. Based on our analyses in chapter 5, increased levels of non-occupational physical activity seemed to increase the probability of reaching the age of 90 years in both men and women. In men, we observed a positive linear association, indicating that probabilities of reaching longevity increase with increasing levels of physical activity. In women, we observed a plateau, indicating that the potential beneficial effect of physical activity is restricted to a certain amount in terms of reaching longevity. In earlier studies, BMI showed significant inverse associations with longevity in both extremes of the spectrum (<20 kg/m2 and >30 kg/m2), but the use of varying BMI cut-off points made it difficult to draw clear conclusions (2, 5, 7, 9). In the analyses of chapter 5, underweight (BMI<18.5 kg/m2), and obesity (BMI ≥30 kg/m2) were associated with a reduced probability of reaching 90 years of age, but only in women. In men, no association was observed between BMI and reaching longevity. After excluding ex-drinkers, moderate alcohol consumption (5-<15 gr. alcohol per day) at the age of 68-70 years was associated with the highest probability of reaching the age of 90 years in both men and women (chapter 6). Earlier studies found inconsistent results regarding the association between alcohol consumption and longevity as presented in chapter 2. The effect estimates observed in chapter 6 did indicate that binge drinking was associated with lower chances of reaching longevity.
Based on the analyses described in chapter 7, we observed no association between indicators of menstrual timing (age at menarche, age at menopause, and reproductive lifespan) and the likelihood of reaching longevity. We did observe that a later age at first childbirth was associated with an increased probability of reaching the age of 90 years. The use of Hormone Replacement Therapy was also positively associated with reaching longevity, but only in women with an early menopause (<age 50 years).

Based on the analyses of chapter 8, no significant associations were observed between loneliness and reaching 90 years in both men and women. When we considered the sub dimensions of loneliness (emotional and social loneliness) we observed that social loneliness was significantly inversely associated with reaching 90 years in women.

Interpretation of main findings
In line with earlier studies, in chapter 3 we observed that offspring of long-lived parents have a higher likelihood of becoming long-lived themselves. We have hypothesized that this relationship is explained by a combination of early environmental influences and genetic factors. After further adjustment of environmental factors, we observed strong evidence for the existence of a specific mother-daughter longevity relationship. Other studies also observed strong evidence for a mother-daughter longevity relationship. These consistent findings could hint towards an important role of variations in inherited mitochondrial DNA (mtDNA) in the process of reaching longevity, which is transmitted via the maternal germline only (13). Indeed, several studies have found an association between longevity and mtDNA variants of haplogroup J in several European countries (14-16), and with mtDNA variant haplogroup D in Japan (17). In these studies, it was observed

that these haplogroups were more common among centenarians than in ethnically matched younger controls. Later studies observed that cells that contained mtDNA belonging to haplogroup J produced less reactive oxygen species (ROS) and less adenosine triphosphate (ATP), compared to cells containing other mtDNA molecules, which could explain a decreased rate of somatic aging. However, these findings could not be replicated in other geographical populations, which indicates that the effect of certain mtDNA variations depend on the individual genetic background (18). This hypothesis was later tested and confirmed when looking at specific mutation patterns in mtDNA (19). Consequently, more advanced analyses techniques are needed to study the interplay between haplogroups and individual mutations to adequately assess the relationship between mtDNA and reaching longevity.

We also observed evidence for the presence of a father-son longevity relationship. However, because other studies did not observe such a relationship, this finding should be further explored. Although the genetic traits observed in long-lived families are beneficial at an individual level, some researchers argue that these stable genomes could be disadvantageous for the successful evolution of the species, on a population level (20). It has been observed that individuals aged 80 years and over had a lower percentage of chromosomal aberrations, compared to younger controls (21). It seems that the genome of these individuals seems to be more resilient against DNA mutations, resulting in a slower rate of cell senescence. However, with lower genetic instability, individuals are less adaptable to potential environmental changes, which reduces the evolutionary ability of the species (20). Therefore, at a population level, lifestyle or environmental modifications could be a more favorable strategy to promote longevity.

As described in chapter 1, environmental factors account for about 75% in the process of reaching longevity. Based on earlier studies (1-12) and the result of our analyses, smoking seems to be the single most important determinant for reaching exceptional ages in both men and women. Men who had never smoked more than doubled their chances of reaching 90 years of age compared to men who were still smoking at older ages. Quitting smoking seemed to improve the likelihood of reaching longevity, but still, the chance of reaching an exceptionally old age was smaller compared to those who had never smoked. We also observed that the association between smoking and longevity was stronger in men than in women. This is most likely explained by differences in smoking behaviour between both sexes (e.g. smoking quantity and type of cigarettes). It is hypothesized that exposure to tobacco could decrease the likelihood of reaching longevity by acting as an accelerator of the aging process, and by increasing the risk for several diseases of which smoking is a recognized risk factor (22). It is known that tobacco smoke contains high levels of free radicals that are produced in a steady state by the oxidation of NO to NO2, which then reacts with reactive species in smoke such as isoprene (23). Furthermore, it has been observed that plasma levels of antioxidant vitamins were lower in smokers, compared to never smokers, and that these levels increased with smoking cessation (24). The additional accumulation of free radicals, in combination with lower plasma levels of antioxidants, may accelerate the aging

process by increasing the oxidative stress in somatic cells. Furthermore, it has been observed that smoking was associated with shortening of telomeres in circulating lymphocytes, which accelerates the deterioration of the immune system associated with aging (immunosenescence) (25). Smoking also increases the risk for developing several diseases, and thus increases the risk for premature mortality, which might also lead to a reduced chance of reaching longevity (26).

Being underweight (BMI <18.5 kg/m2) or obese (BMI ≥30 kg/m2) seemed to reduce the likelihood of reaching longevity in women. Interestingly, in the analyses of chapter 5, BMI showed no association with reaching longevity in men. However, we did observe that a BMI of 25 kg/m2 and above did reduce the probability of reaching 90 years in never and former smoking men, but not in current smokers. Furthermore, the test for interaction of smoking on the relationship between BMI and longevity was statistically significant. The high proportion of current smokers in men, could explain why we did not observe an association between BMI and longevity in men. Only one other longevity study has stratified for smoking status in men, when investigating the relationship between BMI and reaching the age of 85 years (2). It found that the inverse relationship between BMI (≥25kg/m2 vs. <25 kg/m2) and reaching the age of 85 was stronger in non-smokers, compared to current smokers (2). The reason why BMI was not associated with reaching longevity in current smokers remains unclear and should be further explored.

Physical activity was positively associated with reaching longevity in our study, and in studies performed earlier. With aging, the risk of developing cognitive and physical impairments increases, and there is a decline in cardiorespiratory fitness and muscle function (27, 28). It has been shown that regular physical exercise has a beneficial effect on maintaining brain function, cardiovascular function, lung function, muscle function, body composition, and metabolism, as has been summarised in (29). Additionally, physical activity seems to have a positive effect on aging at the cellular level, as summarised in (30). Still, there remains some controversy regarding the optimal duration and intensity of physical activity. In our analyses, the likelihood of reaching 90 years of age increased with an increasing duration of non-occupational physical activity in men. However, in women the likelihood of reaching 90 years increased until around 60 minutes of non-occupational physical activity per day, after which the effect estimates plateaued. Other studies on longevity also showed inconsistent result between duration of physical activity and longevity. Only one study observed a dose-response relation between duration of physical activity and longevity in men (2), while two other studies did not observe such a relationship among men (3, 7). Therefore, the effect of increasing exercise duration on longevity at an older age remains unclear. Regarding intensity, no study has assessed the relationship between the intensity of physical activity and reaching longevity thus far. It has been observed that extraordinary peaks in physical performance among Olympic athletes in early life was associated with increased mortality rates above the age of 50 years (31). Based on these results, the authors hypothesized that the investments in physical strength and growth in early life come at the cost of somatic maintenance in later life (31). However, this hypothesis

remains speculative and should be further examined in future studies.

There has been a lot of controversy surrounding the association between alcohol consumption and reaching longevity. We observed that moderate alcohol consumption (5-<15 gr. alcohol per day) was associated with the highest probability of reaching longevity in both men and women. Other studies observed no relationship (1, 7) or an inverse relationship (9, 12) between alcohol intake and reaching longevity. Regarding premature mortality, a J-shaped relationship between alcohol intake and premature mortality was observed (32). This indicates that the relationship might be dose-dependent, with favourable effects at lower alcohol dosages, and negative effects at higher alcohol dosages. Heavy alcohol consumption is associated with detrimental effects on the brain, cardiotoxicity, and with an increased risk for developing several types of cancer and liver disease (33-36). Mild or moderate alcohol intake has been associated with a decreased risk for cardiovascular diseases, and diabetes type II (37, 38). While alcohol exposure seems to have opposite effects on disease development, some animal studies also suggest a direct beneficial effect of exposure to alcohol on the aging process. In one study, an association was observed between alcohol administration and increased FOXO3A activity in mouse liver (39). Single nucleotide polymorphisms in the FOXO3A is one of the most important genetic alterations linked with reaching longevity in humans (40, 41). Furthermore, one study observed an association between moderate alcohol intake and a downregulation of mTOR activity in the myocardium of Yorkshire swine (42). The mTOR nutrient sensing pathway is often linked with longevity, but findings are inconclusive (40).

In accordance with the evolutionary theories described in chapter 1, it is hypothesized that investments in growth and reproduction would result in a decreased maintenance of somatic cells in later life. Several researchers have tried to test this hypothesis in humans, but it has led to contradictory results. To date, most studies have used historical data to study populations under natural fertility conditions (43). Most of these studies looked at the number of childbirths and its association with reaching longevity and found no clear evidence for the existence of such relationship, as summarised in (43). Regarding evidence from prospective cohort studies, there is also no conclusive evidence of an existing reproductive trade-off in humans. A study by Shadyab et al. (2016) observed that a later age at menarche, a later age at menopause, and a longer reproductive lifespan were associated with an increased odds of reaching 90 years, which would conflict with the evolutionary theories described earlier (44, 45). Furthermore, in later analyses they observed that parity was positively associated with reaching longevity, which would also indicate that increased reproductive investments would not reduce somatic maintenance leading to a decreased chance of reaching longevity (46). In contrast to the findings of Shadyab et al. (2016), in our analyses (chapter 7), we did not observe any association between timing of menarche, menopause, reproductive lifespan and parity and reaching longevity. This illustrates that the relationship between reproduction and reaching longevity in humans remains inconsistent and needs to be further explored.

In our analyses, loneliness was not significantly associated with reaching longevity. This was surprising given the observed significant association between loneliness and mortality in earlier studies (47). However, the current lack of publications on the relationship between loneliness and longevity makes it difficult to reflect on. Our finding could illustrate that a risk factor associated with mortality does not have to be necessarily associated with longevity as well, as we did explain in Chapter 1. Alternatively, there is also the possibility that our observation is a chance finding, and replication is desirable.

Old but healthy?

With an increasing life expectancy, there is also an increasing interest in the quality of life during these added years to life. Many elderly people experience an increasing burden of disease with aging. As a result, several new concepts have been developed that tried to quantify a measure for an increasing lifespan free of disease. Terms like healthy life expectancy, healthy aging, or successful aging, have incorporated quantitative indicators of disease prevalence, mental functioning and/or physical functioning together with chronological aging (48, 49) .Even though the life expectancy has been increasing, data suggests that increases in healthy lifespan are developing more slowly (50). Unlike the treatment of communicable diseases in the first half of the twentieth century, improvements in treatment options for non-communicable diseases have mostly led to improved survival rates, rather than decreases in the prevalence of disease. As a result, the average duration of the disease increased, and the prevalence of non-communicable disease increases with age (51). Consequently, the increasing life expectancy in the second half of the twentieth century was accompanied with an increasing burden of chronic diseases (51).

Although the healthy life expectancy seems to increase more slowly compared to the period life expectancy, reaching longevity has been associated with a delayed occurrence of morbidity (52). It was observed that long-lived individuals (95+ years) experienced age-related diseases (incl. cancer, cardiovascular disease, diabetes mellitus, hypertension, osteoporosis and stroke) on average 18 to 24 years later compared to their younger control group (52). The mechanism behind these findings are still unclear, and replication of these findings in a longitudinal setting is needed. However, the findings do indicate that long-lived individuals are a potentially suitable model to study factors that might contribute to healthy aging. Several studies have shown that determinants that are associated with reaching longevity are often a good predictor for healthy survival or morbidity-free survival as well (10, 11, 53).

Maximum lifespan

Even though more people reach exceptionally high ages, there is still a lot of uncertainty whether there is a fixed maximum attainable lifespan, or that this also increases. In the literature, there exists a controversy about the upper limit to human lifespan. Dong et al. (2016) suggested that there is a natural limit to the human

lifespan, which they estimated to be around 115 years (54). This publication has led to fierce debates about whether a limit to human lifespan exists. The statistical methods used for the publication by Dong et al. has been criticized by other researchers (55-58), and another study suggests that there is a plateau, but no limit to the human lifespan (59). Predictions and theories about the maximum lifespan, are largely influenced by the oldest individuals ever recorded. The oldest "officially" documented human individual is Jeanne Calment, who died in 1997 at an age of 122 years (60). There is still a lot of controversy whether her record is valid, or whether this was a case of identity fraud between mother and daughter (61, 62). The uncertainty around this influential case (outlier) has a huge impact on the debate surrounding the theoretical and statistical modelling of the maximum lifespan. Despite the many speculations on whether a maximum lifespan exists, in the end, only time will tell whether the current record can be broken.

Methodological considerations

The analyses presented in this thesis have several strengths and limitations to consider that might have influenced the validity of our findings. Furthermore, there are some additional methodological points that we have to discuss.

Internal & external validity

Important strengths of the analyses presented in this thesis are the longitudinal study design, the large sample size, and completeness of follow-up. In comparison with other observational study designs used before (e.g. historical cohorts, case-control design), using a prospective cohort approach reduces the risk for information bias, and selection bias because the exposure has been determined independently before the outcome was measured. Furthermore, we were able to collect extensive data on potential confounding variables, making it possible to adjust for an elaborate set of variables, reducing the risk for bias due to confounding. The large sample size made it possible to conduct analyses on several lifestyle habits (e.g. smoking and drinking habits) in great detail. The high completeness of follow-up decreases the risk for selective dropout of participants.

One limitation of the analyses presented in this thesis is that the analyses were based on a single baseline measurement. For instance, no information was collected on changing smoking habits after baseline measurement. Although few people will start smoking at an older age, more people will quit while aging (63). Some cohort members might have quit smoking during follow-up, but would still be classified as a current smoker in our analyses. This might have led to an underestimation of the effect of smoking on longevity. Furthermore, BMI could have varied before and after the baseline measurement. Although we expect that our baseline measurement is a fairly good representation of weight during most of the lifespan, ideally weight should be measured at different time periods. The potential problem of reverse causation arises as well. Although we collected information on disease status at baseline, some baseline characteristics might be explained by the participants' preclinical disease status. For example, persons who develop a lethal or chronic disease in the years after baseline measurement, and therefore are less likely to

reach longevity, might already have some preclinical symptoms before or at baseline, including changes in weight, or a reduced level of physical activity. In our analyses on alcohol consumption, we were able to exclude ex-drinkers who had quit drinking alcohol up to five years before the baseline measurement, to account for reverse causation.

It should also be noted that the participants included in most of the analyses already survived to advanced ages (e.g. 68-70 years at baseline). This could have resulted in potential survivorship bias for some analyses. For instance, those who are especially vulnerable for the adverse effects of smoking might already have died before reaching the age of 68 years. As a result, the association between smoking and reaching longevity might be even stronger in younger cohorts.
The chance of reaching the age of 90 years (at the age of 68-70 years) in the NLCS longevity cohort was 15.5% for men, and 33.4% for women. This was slightly higher than the estimations given by Statistics Netherlands. They estimated that men and women aged 69 in 1990 had a 12.0%, and 28.0% chance to reaching the age of 90 years, respectively (64). As a result, one could argue that the participants of the NLCS may have been more healthy, compared to the general Dutch population. However, the estimations of Statistics Netherlands were based on the current mortality rates of 1990 in a hypothetical cohort. As a result, these estimates do not take the improved mortality rates between 1990 and 2011 into account. This illustrates that the period life expectancy might lead to an underestimation of the true survival probabilities, compared to a real cohort that is longitudinally followed over time.

Regarding the analyses on reproductive factors, the prevalence and timing of oral contraceptive (OC) use in this study population are not comparable with current generations, which limits the external validity of our findings regarding OC use and longevity to current generations. In modern generations the use of birth control is much more common. The longevity cohort of the NLCS was situated in an era where various forms of birth control were gradually introduced, and therefore not yet fully integrated. However, later generations have not been able to reach longevity yet. Therefore, future studies are needed to investigate the potential impact of birth control on the relationship between reproductive factors and reaching longevity.

Regarding the analyses on loneliness, the ages at which the participants were included was much broader (ages 64-85). This means that there are some potential generational differences between the participants. Furthermore, older individuals have a higher (conditional) chance of reaching 90 years of age at baseline. We did account for this potential confounding effect by adjusting, and stratifying for baseline age in the multivariable-adjusted models. However, because of the limited sample size, we were only able to stratify by age categories of 10 years. Therefore, residual confounding by baseline age could still have influenced our results. Preferably, future studies should use homogenous age groups when the sample size allows for that, as we did in the NLCS analyses. This limits the risk for

(confounding) bias due to potential age and generational differences.

Comparison of the statistical analysis techniques
Earlier studies estimated the association between lifestyle factors and longevity using logistic regression analyses. However, given the high proportion of participants that have reached longevity (90 years of age) in our study population, odds ratios (OR) easily overestimate the effect compared to risk ratios (65). Given the high proportion of the outcome and the prospective cohort design, which makes it possible to estimate incidences of reaching longevity, multivariable-adjusted Risk Ratios (RR) were preferred over the use of ORs. Therefore, we searched for alternatives to calculate RR instead of OR which yielded several options, which we have compared (Table 1).

Firstly, the use of a log-binomial regression model was considered. This is "theoretically" the most suitable alternative. However this model often fails to converge when analyzing small samples or using multiple confounders. We experienced that this model was problematic when analyzing relationships in more detail, with smaller sample sizes.

Secondly, the Poisson regression model was considered. The results of the Poisson regression model were identical to the results of the log-binomial regression model in larger samples, and the model yielded no problems when analyzing smaller sample sizes (Table 1). Lastly, the Cox regression model with a fixed follow-up time was considered. This method performed similar to the Poisson regression model (Table 1). This technique differs from the Cox proportional hazards model, because we use a fixed follow-up time for each participant. When calculating a Hazard Ratio (HR), use is being made of an average risk over a certain time period (based on person-time). When using a fixed follow-up time, time is not taken into account by appointing an equal follow-up time to each participant. As a result a cumulative risk is estimated, that can be translated to a Risk Ratio instead of a Hazard Ratio.

Concluding remarks and future perspectives
The research presented in this thesis aimed to identify several (modifiable) factors that are associated with reaching the age of 90 years. We observed that offspring of parents who survived to ages 80 year and older had an increased likelihood of reaching the age of 90 years. Furthermore, smoking was the most important (modifiable) factor associated with a decreased probability of reaching the age of 90 years, while being physically active, having a BMI between 18.5 and 25.0 kg/m2 (in women), and a moderate alcohol consumption (5-<15 gr. alcohol/day) were associated with increased probabilities of reaching the age of 90 years.

Table 1: Comparison of effect sizes on the relationship between smoking habits and reaching longevity, using different statistical analyses techniques.

	n	90+	Logistic regression (OR)	Log-binomial regression (RR)	Poisson regression (RR)	Cox regression (fixed follow-up) (RR)
Cigarette smoking status in men (age-adjusted)						
Never smoker	305	78	3.35 (2.34-4.83)	2.75 (2.03-3.73)	2.75 (2.03-3.73)	2.75 (2.03-3.73)
Former smoker	955	161	1.98 (1.46-2.70)	1.82 (1.38-2.39)	1.82 (1.38-2.39)	1.82 (1.38-2.39)
Current smoker	679	63	1	1	1	1
Cigarette smoking status in men with higher vocational/ university education (fully-adjusted model)						
Never smoker	66	21	2.02 (0.72-5.62)	Failed to converge	1.77 (0.87-3.62)	1.77 (0.87-3.62)
Former smoker	111	29	1.60 (0.51-4.98)	Failed to converge	1.46 (0.66-3.21)	1.46 (0.66-3.21)
Current smoker	74	10	1	1	1	1

The field of longevity research using individual longitudinal data is relatively new and still expanding. Therefore, more research is needed to further identify characteristics that are associated with reaching longevity, and to replicate the findings we described earlier. Currently, there are only few prospective cohort studies that have a sufficiently long follow-up to study longevity of their participants. Fortunately, their number is growing, which opens new possibilities to study the determinants of reaching longevity.

Based on the results of this thesis we observed that some modifiable lifestyle factors, including smoking and physical activity, show a strong association with reaching longevity in our study population. In the past, it has been observed that smoking had a strong effect on life expectancy, especially in men (66). It is suggested that the sex difference in life expectancy that was observed in the twentieth century is mainly caused by differences in smoking behavior (66). More recently, data from the USA and UK suggest that the increase in life expectancy has started to plateau (67, 68). It has been suggested that the growing number of obese and physically inactive individuals could have caused the stagnating life expectancy (69, 70). Longitudinal cohorts using individual data can be used to quantify the relationship between such lifestyle factors and lifespan, as we did in our analyses for this thesis. Because predictions on the development of the life expectancy are often based on simple linear extrapolation of a historical period (71), it is difficult to predict the impact of changing lifestyle trends on future life expectancy. More recently, efforts have been made to forecast lifestyle-attributable mortality in the future, using epidemiological data e.g. (72). In the long-term, these developments might lead to better projections of the future life expectancy, considering the influence of changing lifestyle trends.)

Apart from alcohol intake, little attention has been given to the relationship between nutrition and longevity in this dissertation. As described in chapter 2, there is a lack of prospective studies investigating the relationship between nutrition and longevity in humans. Unfortunately, we did not have the opportunity to investigate

this relationship during the time frame of this PhD project. Interestingly, caloric restriction is often mentioned as a potential intervention strategy to prolong the lifespan in humans. However, most of these claims are based on the results of animal studies (73). There is still a lot of debate whether caloric restriction would also prolong the lifespan in humans (74). Studying the effects of caloric restriction on longevity in humans is difficult, due to ethical concerns it would raise. Furthermore, cohorts that have data on individuals who experienced a period of caloric restriction are rare. In some cohorts, including the NLCS, information of individuals who experienced a period of caloric restriction is available (75, 76). Therefore, it would be interesting to evaluate the relationship between caloric restriction and longevity using information of these cohorts in future studies.

Although the number of studies is growing, there is still a lot of inconsistency and debate regarding the relationship between reproduction and lifespan in humans. We observed that the results of observational studies among humans do not correspond with the hypotheses of evolutionary theories of aging, including the disposable soma theory, and the theory of antagonistic pleiotropy. Furthermore, the recent advances in birth control could also change the relationship between reproduction and lifespan. It will be interesting to see how these relationships will evolve in the near future.

In chapter 2, we mentioned that the baseline cut-off ages and longevity cut-off ages varied widely across the different longevity studies. In our own analyses, we did observe that the effect estimates between a risk factor and longevity, might differ using different longevity cut-off ages. For instance, we observed that the strength of the association between smoking and longevity became stronger with increasing longevity cut-off age (3)(Chapter 4). Furthermore, in the analyses on loneliness and longevity using data from the LASA cohort, we also observed that the association between loneliness and longevity might differ at different baseline ages. Given the long follow-up and complexity it requires to study the etiology of longevity in a longitudinal setting, studies are restricted to a certain time window in the lifespan. Ideally, one might study longevity using a conception-to-death cohort design that starts during pregnancy until death, with multiple follow-up measurements in between (77). However, such a study design will not be feasible in the near future, given the long follow-up and logistic complexity (77). Alternatively, advances in the field of life course epidemiology could provide relevant opportunities to address the issues currently experienced with the use of multiple cut-off ages. Life course epidemiology aims to study the contribution of early life factors together with later life factors to estimate the risk and protective processes on several outcomes across the life course (78). For this, (combined) longitudinal information of existing and new longitudinal cohorts is needed to cover different time windows during the life course. Because prospective cohort studies only provide results on the long term, acquiring funding is difficult when competing with different types of studies delivering results on the short term (79). This threatens the long-term sustainability of existing and newly developed cohorts, and a more strategic approach is needed to ensure that there is more support for these types of studies.

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Addendum

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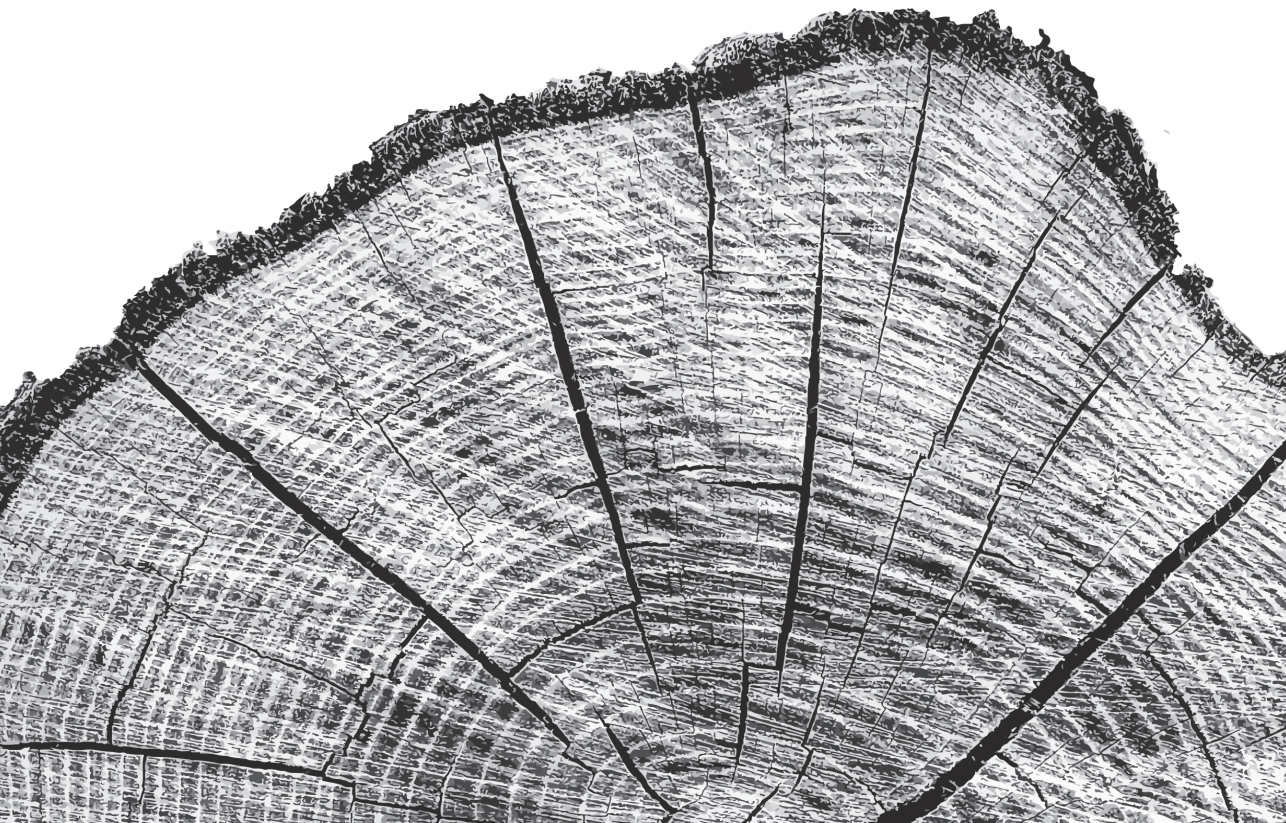

Summary

In this dissertation, we have investigated factors that are associated with reaching the age of 90 years (longevity). To investigate these relationships, we used data from the Netherlands Cohort Study (NLCS) and the Longitudinal Aging Study Amsterdam (LASA).

For the analyses in which the association between parental, lifestyle and reproductive factors and reaching the age of 90 were investigated, we used data from the NLCS. The NLCS was set up in 1986 as a large prospective cohort study, which aimed to investigate the relationship between diet and the development of multiple forms of cancer in the Netherlands. The NLCS collected data from 120,852 men and women (55-69 years) using an 11-page self-administered questionnaire. This questionnaire contained questions about demographic factors, dietary habits, smoking habits, physical activity, alcohol consumption, anthropometry, medical information and family history. Because at the start of these analyzes only a part of the participants were able to reach the age of 90, we have limited our analyses to the oldest birth cohorts (1916 and 1917) of the NLCS cohort. The participants (68-70 years at the start of this study) from these two birth years form the cohort for the analyses in this dissertation. Follow-up of this cohort up to the age of 90 was 99.9% complete. The analyses in this thesis are based on 7,807 participants (3,646 men and 4,161 women). Among these participants we observed that 565 men (15.5%) and 1388 women (33.4%) survived until the age of 90.

In **chapter 3** we observed that both male and female descendants of parents who survived up to 80 years of age had an increased chance of reaching the age of 90, compared to those whose parents had died before the age of 80. We suggested that this benefit could be passed on to later generations through a combination of early environmental influences and genetic factors. We have therefore corrected the estimates for some environmental factors that could explain the observed relationship. In these analyses, a longer lifespan of fathers in male offspring and a longer lifespan of mothers in female offspring was still associated with an increased chance of reaching the age of 90.

With regard to lifestyle factors, our analyses focused on smoking behavior, height, BMI, non-occupational physical activity and alcohol consumption. Our analyses in **chapter 4** showed that current and former smokers have a considerably lower chance of reaching the age of 90 compared to never-smokers. In addition, we observed that this relationship was stronger in men compared to women. In further analyses, we found that this difference could possibly be attributed to the differences in smoking behavior (incl. smoking quantity, and type of tobacco).

Based on our analyses in **chapter 5**, an increasing level of (non-occupational) physical activity seemed to increase the chance of reaching the age of 90 in both men and women. In men, we observed a positive linear association, indicating that the chance of reaching longevity increased with an increasing level of physical

activity. In women, we saw that the potential beneficial effect of physical activity is limited to a certain amount of physical activity (~ 60 min./day) in terms of achieving longevity, after which the chances did not increase further. Furthermore, in the analyses of **chapter 5**, underweight (BMI <18.5 kg / m2) and obesity (BMI ≥30 kg / m2) were associated with a reduced chance of reaching 90 years, but only among female participants. In men, no relationship was observed between BMI and reaching the age of 90.

After excluding former drinkers, moderate alcohol consumption (5- <15 g alcohol per day) at the age of 68-70 years was associated with the highest probability of reaching the age of 90 in both men and women (**chapter 6**). The effect estimates observed in **chapter 6** further indicated that binge drinking was associated with lower chances of achieving longevity.

Based on the analyses described in **chapter 7**, we did not observe a relationship between indicators of the fertile period (age at menarche, age at menopause and reproductive life) and the chance of reaching a 90-year-old age among female participants. We found that a later age at the first delivery was associated with an increased chance of reaching the age of 90. The use of hormone replacement therapy was also positively associated with reaching longevity, but only in women with early menopause (<50 years).

For the analyses of loneliness in relation to reaching the age of 90, we used data from the LASA cohort. LASA is a prospective cohort study that was initiated in 1992 to study the physical, emotional, cognitive and social functioning of elderly people (55-84 years) in the Netherlands. For this, potential participants were approached from 11 municipal registers from representative geographical regions in the Netherlands for the Living Arrangements and Social Networks of Older Adults (LSN) program. Participants recruited for this study were born between 1908 and 1937 (n = 3,805). From this sample, 3,677 (still living) participants were contacted for the first LASA cycle (1992-1993), on average 11 months after the LSN interview, with a response rate of 85%. The examinations took place at the participants' home, approximately every three years. Trained interviewers conducted interviews and additional data was obtained using a questionnaire. During the interviews, the participants were also asked for permission to participate in a separate medical interview. Clinical measurements were taken during the medical interview and the interviewer asked additional questions. Loneliness was measured during the interviews using a validated 11-item De Jong-Gierveld scale. Because only a part of the full cohort could have reached the age of 90 at the start of these analyses, the analyses were limited to participants born before 2 August 1928. Follow-up of this cohort up to the age of 90 was 99.5% complete. After excluding participants with missing data on loneliness (n = 62), 1,032 men and 1,078 women were used for these analyses. Our follow-up showed that among these participants 252 men (24.4%) and 413 women (38.3%) have reached the age of 90 years.

Based on the analyses of **chapter 8**, no significant associations were observed

between loneliness and reaching the age of 90 in both men and women. When we looked at the subdimensions of loneliness (emotional and social loneliness), we saw that social loneliness was significantly negatively associated with reaching 90 years in women.

In the systematic literature study from **chapter 2**, we concluded that smoking and a low level of physical activity were associated with a lower chance of achieving a long life. This is in line with the results that we observed in **chapters 4 and 5**. Alcohol intake and BMI showed limited and / or conflicting associations with reaching longevity. In addition, the review revealed that the age at which the parents died was positively associated with reaching longevity, with the age at which the mother died showing the strongest association. Some studies indicated a stronger effect of parental lifespan in female offspring compared to male offspring.

Nederlandse samenvatting

In dit proefschrift hebben we onderzoek gedaan naar factoren die geassocieerd zijn met het bereiken van een 90-jarige leeftijd (langlevendheid). Om deze verbanden te onderzoeken hebben we gebruik gemaakt van gegevens afkomstig uit de Nederlandse Cohort Studie (NLCS) en de Longitudinal Aging Study Amsterdam (LASA).

Voor de analyses waarin de associatie tussen ouderlijke-, leefstijl- en reproductieve factoren en het bereiken van een 90-jarige leeftijd is onderzocht, hebben we gebruik gemaakt van gegevens uit de NLCS. De NLCS is in 1986 opgezet als een groot prospectief cohortonderzoek, dat gericht was op het onderzoeken van de relatie tussen voeding en de ontwikkeling van meerdere vormen van kanker in Nederland. De NLCS heeft daarvoor gegevens verzameld van 120.852 mannen en vrouwen (55-69 jaar) met behulp van een zelf gerapporteerde vragenlijst van 11 pagina's. Deze vragenlijst bevatte vragen over demografische factoren, voedingsgewoonten, rookgewoonten, lichamelijke activiteit, alcoholgebruik, antropometrie, medische informatie en familiegeschiedenis. Omdat bij aanvang van deze analyses slechts een deel van de deelnemers in het NLCS cohort de leeftijd van 90 jaar heeft kunnen bereiken, hebben we onze analyses beperkt tot de oudste geboortecohorten (1916 en 1917) van het NLCS-cohort. De deelnemers (68-70 jaar oud bij aanvang van deze studie) uit deze twee geboortejaren vormen het cohort voor de analyses in dit proefschrift. Follow-up van dit cohort tot de leeftijd van 90 was voor 99,9% compleet. De analyses in dit proefschrift zijn dat ook gebaseerd op 7.807 deelnemers (3.646 mannen en 4.161 vrouwen). Onder deze deelnemers zagen we dat 565 mannen (15,5%) en 1388 vrouwen (33,4%) overleefden tot de leeftijd van 90 jaar.

In **hoofdstuk 3** zagen we dat zowel mannelijke als vrouwelijke nakomelingen van ouders die tot 80 jaar en ouder overleefden een verhoogde kans hadden om de leeftijd van 90 jaar te bereiken, in vergelijking met degenen wiens ouders vóór de leeftijd van 80 jaar waren overleden. We stelden voor dat dit voordeel zou kunnen worden doorgegeven aan latere generaties door een combinatie van vroege omgevingsinvloeden en genetische factoren. Daarom hebben we de schattingen gecorrigeerd voor enkele omgevingsfactoren die de waargenomen relatie zouden kunnen verklaren. In deze analyses was de levensduur van vaders bij mannelijke nakomelingen en de levensduur van moeders bij vrouwelijke nakomelingen nog steeds significant positief geassocieerd met een verhoogde kans om de leeftijd van 90 jaar te bereiken.

Met betrekking tot leefstijlfactoren hebben onze analyses zich gericht op rookgedrag, lengte, BMI, niet-beroepsmatige lichamelijke activiteit en alcoholgebruik. Onze analyses in **hoofdstuk 4** toonden aan dat huidige en voormalige rokers een aanzienlijk kleinere kans hebben om de leeftijd van 90 jaar te bereiken in vergelijking met nooit-rokers. Daarnaast observeerden we dat deze relatie sterker was in mannen ten opzichte van vrouwen. In verdere analyses vonden we dat dit verschil mogelijk is toe te wijzen aan de verschillen in rookgedrag (o.a. hoeveelheid

en type tabak).

Op basis van onze analyses in **hoofdstuk 5** leek een toenemende mate van (niet-beroepsmatige) lichamelijke activiteit de kans te vergroten om de leeftijd van 90 jaar te bereiken bij zowel mannen als vrouwen. Bij mannen zagen we een positieve lineaire associatie, wat aangeeft dat de kans om een lange levensduur te bereiken toenam met een toenemende mate van fysieke activiteit. Bij vrouwen zagen we dat het potentiële gunstige effect van fysieke activiteit beperkt is tot een bepaalde hoeveelheid lichamelijke activiteit (~60 min./dag) in termen van het bereiken van een lange levensduur, waarna de kansen niet verder toenamen. Verder werden in de analyses van **hoofdstuk 5** ondergewicht (BMI <18,5 kg/m2) en obesitas (BMI ≥30 kg/m2) geassocieerd met een verminderde kans om 90 jaar te worden, maar alleen bij vrouwelijke deelnemers. Bij mannen werd er geen verband gevonden tussen BMI en het bereiken van 90-jarige leeftijd.

Na uitsluiting van voormalige drinkers werd matig alcoholgebruik (5-<15 gr. alcohol per dag) op de leeftijd van 68-70 jaar geassocieerd met de hoogste kans om de leeftijd van 90 jaar te bereiken bij zowel mannen als vrouwen (**hoofdstuk 6**). De effectschattingen waargenomen in **hoofdstuk 6** gaven verder aan dat binge-drinken geassocieerd was met lagere kansen op het bereiken van een lange levensduur.

Op basis van de analyses beschreven in **hoofdstuk 7**, hebben we geen verband geobserveerd tussen indicatoren van de vruchtbare periode (leeftijd bij menarche, leeftijd bij menopauze en reproductieve levensduur) en de kans op het bereiken van een 90-jarige leeftijd onder de vrouwelijke deelnemers. We hebben geconstateerd dat een latere leeftijd bij de eerste bevalling was geassocieerd met een verhoogde kans om de leeftijd van 90 jaar te bereiken. Het gebruik van hormoonsuppletietherapie was ook positief geassocieerd met het bereiken van een lange levensduur, maar alleen bij vrouwen met een vroege menopauze (<50 jaar).

Voor de analyses naar eenzaamheid in relatie tot het bereiken van de 90-jarige leeftijd hebben we gebruikt gemaakt van gegevens afkomstig uit het LASA cohort. LASA is een prospectieve cohortstudie die in 1992 is gestart om het fysieke, emotionele, cognitieve en sociale functioneren van ouderen (55-84 jaar) in Nederland te bestuderen. Hiervoor werden mogelijke deelnemers benaderd uit 11 gemeente registers uit representatieve geografische regio's in Nederland voor het programma Living Arrangements and Social Networks of Older Adults (LSN). Deelnemers die voor deze studie werden aangeworven, werden geboren tussen 1908 en 1937 (n = 3.805). Uit deze steekproef werden 3.677 (nog levende) deelnemers gecontacteerd voor de eerste LASA-cyclus (1992-1993), gemiddeld 11 maanden na het LSN-interview, met een responspercentage van 85%. De onderzoeken werden bij de deelnemers thuis afgenomen welke ongeveer om de drie jaar plaatsvonden. Getrainde interviewers hielden interviews en aanvullende gegevens werden verkregen met behulp van een vragenlijst. Tijdens de interviews werd aan de deelnemers ook toestemming gevraagd om deel te nemen aan een afzonderlijk medisch interview.

Tijdens het medisch interview werden klinische metingen verricht en stelde de interviewer aanvullende vragen. Eenzaamheid is gemeten tijdens de interviews met behulp van een gevalideerde 11-item De Jong-Gierveld schaal. Omdat slechts een deel van het volledige cohort de leeftijd van 90 jaar kon bereiken, waren de analyses beperkt tot deelnemers die zijn geboren vóór 2 augustus 1928. Follow-up van dit cohort tot de leeftijd van 90 was voor 99,5% compleet. Na uitsluiting van deelnemers met ontbrekende gegevens over eenzaamheid (n = 62), werden 1.032 mannen en 1.078 vrouwen gebruikt voor deze analyses. Onze follow-up toonde aan dat onder deze deelnemers 252 mannen (24,4%) en 413 vrouwen (38,3%) de leeftijd van 90 jaar hebben bereikt.

Op basis van de analyses van **hoofdstuk 8** werden geen significante associaties waargenomen tussen eenzaamheid en het bereiken van de 90-jarige leeftijd bij zowel mannen als vrouwen. Toen we de subdimensies van eenzaamheid (emotionele en sociale eenzaamheid) in ogenschouw namen, zagen we dat sociale eenzaamheid significant negatief geassocieerd was met het bereiken van 90 jaar bij vrouwen.

In de systematische literatuur studie uit **hoofdstuk 2**, concludeerden we dat roken en een laag niveau van lichamelijke activiteit geassocieerd waren met een lagere kans op het bereiken van een lange levensduur. Dit ligt in lijn met de resultaten die wij observeerden in **hoofdstuk 4 en 5**. Alcoholinname en BMI vertoonden beperkte en/ of tegenstrijdige associaties met het bereiken van een lange levensduur. Daarnaast kwam uit de review naar voren dat de leeftijd waarop de ouders waren gestorven positief geassocieerd was met het bereiken van een hoge leeftijd, waarbij de leeftijd waarop de moeder stierf de sterkste associatie liet zien. Sommige studies wezen op een sterker effect van ouderlijke levensduur bij vrouwelijke nakomelingen in vergelijking met mannelijke nakomelingen.

Valorisation

Introduction

In this chapter we will discuss the relevance, and value of this dissertation for society. Valorisation creates value from research by describing how research results can be used for economical and/or societal benefit, or by translating the acquired knowledge into new products, services, processes, or business (1).

Valorisation during the PhD trajectory

The study findings presented in this dissertation have not only been published in several international scientific journals, but were also communicated to a broader audience. In 2017, and 2018, we presented our study results at the Dutch Demography Day. This is an annual meeting organized by the Netherlands Demographic Society, to communicate the latest research findings in the field of demography in the Netherlands. In 2017, 2018, and 2019 our study findings were displayed and presented at the Dutch Epidemiological Conference (WEON), to an audience consisting mostly of epidemiologists. Our study results were also presented at the European Congress of Epidemiology (Lyon, France) in 2018. Additionally, in 2019 and 2020, our study results on body size, non-occupational physical activity and reaching longevity, and alcohol consumption and reaching longevity were picked up by several international newspaper, television and radio organizations, e.g. Newsweek, CNN, and The Times (of London), and were widely spread in printed and online media formats, worldwide. As a result, our research findings were spread to a broad (lay) audience worldwide. Communicating our results at several (international) conferences and in the media has hopefully contributed to an increased awareness of several determinants of reaching (human) longevity among professionals and the general public.

Future Valorisation

The findings presented in this dissertation could contribute to an increased understanding of determinants of reaching longevity at an individual level. Additionally, the results strengthen the knowledge on the relationship between lifestyle and aging, that could be of use in demographic projections, and policy making.

Determinants of longevity

The use of data from long-running prospective cohort studies, has provided a unique opportunity to study the determinants of reaching longevity at an individual level. As described earlier in the Introduction section, until recently most longevity research was performed using population- or retrospective study designs to identify how the exceptional old differ from the rest of the population. Individual data that is prospectively collected to study determinants of longevity is rare and costly, because of the long follow-up it requires until the participants are “at risk” of reaching longevity. However, a prospective cohort design has several methodological advantages including a selection of participants and data collection independent of the outcome, which reduces the risk for selection- and information bias.

Furthermore, the detailed information that is collected on other factors makes it possible to control for potential confounding.

Some modifiable lifestyle characteristics were strongly related with reaching longevity. Smoking was the most important factor associated with a decreased chance of reaching longevity, while being physically active, having a BMI between 18.5 and 25.0 kg/m2 (in women), and a moderate alcohol consumption (5-<15 gr. alcohol/day) were associated with an increased chance of reaching longevity. This indicates that the chance of attaining an exceptionally old age is potentially modifiable. As a result, promoting certain lifestyle behaviors (e.g. not smoking, increasing physical activity) in later life (65+ years) could add years to life.. However, it should be noted that the observed associations do not necessarily indicate causation, and replication of these findings in other longitudinal cohorts is needed.

Demographic changes

In the past, it was observed that smoking had a huge negative impact on the average life expectancy, especially in men. It is even suggested that the sex difference in life expectancy that was observed in the 20th century is mainly caused by smoking (2). Our analyses confirm that smoking is indeed strongly associated with a shorter lifespan. More recently, data from the USA and UK suggests that the increase in life expectancy has started to plateau, but the reasons behind this stagnation are still unknown (3, 4). It has been suggested that the growing number of obese and physically inactive individuals could have caused the stagnating life expectancy (5, 6). Demographers, and epidemiologists, could utilize our findings to gain a better understanding of the relationship between lifestyle trends in the general population and its potential relationship with demographic changes in the upper limits of human lifespan. Furthermore, predictions on the development of the life expectancy are often based on simple linear extrapolation of a historical period (7). Therefore, it is difficult to predict the impact of changing lifestyle trends on future life expectancy. Using epidemiological data to estimate the lifestyle-attributable mortality in the future could lead to better projection of the future life expectancy in the long-term.

Societal implications

During the dissemination of our results, we got several responses of people who were surprised by the actual probabilities of reaching 90 years, which they had underestimated. Other researchers also indicated that there exists a “disbelief in aging” e.g. (8), in current societies. They argue that there is a profound mismatch between the cultural norms of aging, where most policies are based upon, and the actual lifespan. Increasing probabilities of reaching exceptionally old ages are a positive development on the individual level. However, on a population level, a prolonged lifespan has severe consequences for, for example, existing pension schemes, healthcare facilities and costs, and insurance companies. Policy makers should be aware of these demographic changes, and act on them. Given the design of our study, we were able to present absolute probabilities of reaching 90 years by

the long follow-up of a closed cohort. We believe that these absolute probabilities can inform policy makers about the potential magnitude of aging in subsequent generations, and the potential impact that several determinants might have on these probabilities.

Conclusion

In this dissertation we have performed several quantitative analyses to assess the relationship of several lifestyle, parental and reproductive factors with the likelihood of reaching the age of 90 years (longevity). During the PhD trajectory, there has been a wide dissemination of the results to epidemiologists, demographers, and the lay public. The findings of our analyses contribute to a better understanding of the determinants of reaching exceptionally old ages, which has several implications for the individual and for society.

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Curriculum Vitae

About the Author

Lloyd Brandts was born on October 7th 1989, in Maastricht, the Netherlands. After graduating from secondary school (Bonnefanten college, Maastricht) in 2008, he studied Applied Psychology at Fontys Hogeschool in Eindhoven. In 2011, he started with the bachelor study Health Sciences, with specialization "Prevention and Health" at Maastricht University, which he completed in 2014. During his bachelor study he also participated in the FHML excellence program Maastricht Research Based Learning for Excellence (MaRBLe+) in 2014. Lloyd wrote his bachelor's thesis "The socioeconomic roots of shame and perceptions of social inadequacy" under supervision of Prof. dr. Hans Bosma. Afterwards he started to study Epidemiology at Maastricht University, which he completed in 2015. Lloyd wrote his master's thesis "Associations of muscle composition with short- and long-term treatment complications among colorectal cancer survivors: Findings from the EnCoRe study" under supervision of Dr. Martijn Bours and Prof. Dr. Ir. Matty Weijenberg. After obtaining a MSc degree in Epidemiology he started as a PhD student at the Department of Epidemiology (Maastricht University). He was supervised by Prof. dr. ir. Piet A. van den Brandt, and Prof. dr. Frans W.A. van Poppel to study determinants of reaching human longevity, which resulted in the work presented in this dissertation. The work presented in this dissertation has been published in several international scientific journals and was presented at several national and international conferences. Alongside this research, he was able to gain experience in teaching Epidemiology and Statistics to Bachelor and Master students of Maastricht University. Lloyd currently works as a clinical epidemiologist at Maastricht UMC+ (KEMTA) in Maastricht.

List of Publications

Bosma, H., **Brandts, L**., Simons, A., Groffen, D., & van den Akker, M. (2014). Low socioeconomic status and perceptions of social inadequacy and shame: findings from the Dutch SMILE study. *The European Journal of Public Health*, 25(2), 311-313.
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Parental longevity and the likelihood of reaching longevity in the Netherlands. Cohort Study (NLCS). – WEON 2019, Groningen.
Female reproductive factors and the likelihood of reaching the age of 90 years: The Netherlands Cohort Study – Dutch Demography Day 2018, Utrecht.
Body size, non-occupational physical activity and the chance of reaching longevity in men and women: Findings from the Netherlands Cohort Study. WEON 2018, Bilthoven.
Smoking habits and the chance of reaching longevity in men and women: the Netherlands Cohort Study. Dutch Demography Day 2017, Utrecht.

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Body size, non-occupational physical activity and the chance of reaching longevity in men and women: Findings from the Netherlands Cohort Study. – European Congress of Epidemiology, Lyon (France).
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