Master of Public Health

Master de Santé Publique

Hormonal exposure and walking speed in women in general population. The CONSTANCES study

Aude Laetitia NDOADOUMGUE
Europubhealth 2017-2019, Master II
Specialisation: Epidemiology and Bioastatistics

Location of the practicum:
Centre for research in Epidemiology and Population Health (CESP), INSERM U1018, Villejuif

Professional advisor: Marianne Canonico, CESP

Academic advisor: Olivier Grimaud, EHESP

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

Grateful and thankful to God for all the strength

My profound and heart felt gratitude to everyone who contributed to this work.

I will like to especially thank my professional advisor Dr Marianne Canonico for the opportunity she gave me to work on this project and for her unceasing support and help throughout the internship. I learned a lot working alongside her and her contribution to this work is inestimable.

I want to thank my academic supervisor, Dr Olivier Grimaud for all the feedback, help, contributions and suggestions he provided throughout this work.

Thanks to Dr Alexis Elbaz, the head of the unit for his support and input during working sessions to make this work better.

Thanks to Dr Martine Bellanger, the staff of EHESP and The University of Sheffield for all the help and support throughout the training.

I'll also like to thank Fanny Artaud and Clementine Lemarchand for their encouragements and support throughout my internship.

My gratitude goes out to all the members of the Neuroepidemiology team and Cancer & Environment for the welcoming atmosphere that was present during my internship and for the good moments we shared.

My appreciation goes to Dr Virginie Ringa and her team for their help during the early stages of this work.

Special thanks to Berta, Isabella and Amir for the help and encouragements during the challenging periods and for all the fun, laughter and joyous moments we shared

I am grateful for my Europubhealth family for the mutual support we've provided to each other in the joyful and sad moments. Special thanks to Phyllis, Andrea, Stephanie, Anabelle, Earl, Danytza, Tara, Charles, Mohammed, Carla.

My sisters of MTYT and FF, your unwavering support and prayers have been priceless. My heartfelt thank you to Emmanuelle, Michèle, Arlette, Christelle, Elise, Stephane, Leo, Jan, Albine, HTC family, Joelle M and all my friends back home for your continuous moral support.

Lastly, I would not be here today without the unfailing love, support and prayers of my Mom, Dad, my sister Nathalie, my brothers Serge and Didier, cousins, aunts, uncles and every member of my huge family.

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

WS	Walking speed
HT	Postmenopausal hormone therapy

ABSTRACT

Background: Ageing is characterized by a physiological decline in motor functions associated with an increased risk of disability, hospitalization and death. There is however, significant individual heterogeneity in the evolution of the motor function. There has been a decline in functional capacity of women after menopause but the influence of hormonal exposure on walking speed (WS) remains poorly investigated.

Methods: The analysis focuses on women 45 years and above recruited in the CONSTANCES cohort study in whom a WS test was performed at inclusion. The association of WS with characteristics of reproductive life and use of exogenous hormones were evaluated cross-sectionally using mixed linear and multinomial logistic regressions models.

Results: The analysis sample consisted of 24557 women. The average WS was 173. 1 cm/s. Among all women, age at menarche, number of children and age at first pregnancy were positively associated with WS (β for 1 year= 0.34; 95% CI: 0.15; 0.53, $p < 0.001$, β per child = 0.84; 95% CI: 0.45; 1.24, $p < 0.001$, β for 1 year= 0.24; 95% CI: 0.16; 0.32, $p < 0.001$, for age of menarche, number of children and age at first pregnancy, respectively). On the other hand, menopausal status and use of oral contraceptive pills did not influence walking speed. In menopaused women, similar associations were found for age at puberty, parity and age at first pregnancy. However, age at menopause, type of menopause, duration of reproductive life span, time since onset of menopause and post-menopausal hormonal treatment did not influence WS.

Conclusion: This analysis suggests the existence of hormonal determinants of WS in women over 45 years of age. It would appear that being exposure as late as possible in teenage years and to higher oestrogen concentrations later in adult life may be beneficial on the motor function. These results will have to be confirmed in subsequent studies.

RÉSUMÉ

Contexte. Le vieillissement est caractérisé par un déclin physiologique des fonctions motrices associé à un risque accru de dépendance, d'hospitalisation et de décès. Néanmoins, il existe une importante hétérogénéité inter-individuelle dans l'évolution de la fonction motrice. Il a été observé une baisse des capacités fonctionnelles chez les femmes après la ménopause mais l'influence de l'exposition hormonale sur la vitesse de marche (VM) reste mal connue.

Méthode. L'analyse porte sur les femmes de plus de 45 ans recrutées dans l'étude de cohorte CONSTANCES chez lesquelles un test de la VM a été effectué à l'inclusion. L'association entre les caractéristiques de la vie reproductive, la prise d'hormones exogènes et la VM ont été évaluées transversalement par la mise en œuvre de modèles linéaires mixtes et de régressions logistiques multinomiales.

Résultats. L'échantillon d'analyse comporte 24557 femmes. La VM moyenne était de 173.1 cm/s. Parmi toutes les femmes, l'âge de la puberté, le nombre d'enfants et l'âge à la première grossesse étaient positivement associés à la VM (β pour 1 an=0.34; 95% CI: 0.15; 0.53, p<0.001, β par enfant=0.84; 95% CI: 0.45; 1.24, p<0.001, β pour 1 an=0.24; 95% CI: 0.16; 0.32, p<0.001, pour l'âge de la puberté, le nombre d'enfants et l'âge à la première grossesse, respectivement). En revanche, le statut ménopausique et la prise de pilule n'influençaient pas la VM. Chez les femmes ménopausées, des associations similaires étaient retrouvées pour l'âge de la puberté, la parité et l'âge à la première grossesse. En revanche, l'âge à la ménopause, le type de ménopause, le délai de vie reproductive, le délai depuis la ménopause et le traitement hormonal de la ménopause n'influençaient pas la VM.

Conclusion. Cette analyse suggère l'existence de déterminants hormonaux de la VM chez les femmes de plus de 45 ans. Il semblerait qu'être exposé le plus tard possible à l'adolescence et à des concentrations plus élevées d'œstrogènes plus tard dans la vie adulte puisse être bénéfique sur la fonction motrice. Ces résultats devront être confirmés dans d'autres études.

INTRODUCTION

In 2010, an estimated 524 million people were aged 65 or older (8% of the world's population) and by 2050, this number is expected to nearly triple to about 1.5 billion (16% of the world's population) (1). Developed countries were the most affected in the past as they had the oldest population profile (1) but the dynamic has shifted with a greater proportion of old people now being in developing countries (2). In the absence of disease, there is functional and structural deterioration which occurs in most physiological systems. These changes have an effect on a broad range of tissues, organ systems and functions which can in turn impact the preservation of physical independence in older adults.

The variation in decline of physical function could be due to genetic or environmental determined variability (3). Although the pattern of age-related change for most physiological systems is one of decline, there are some individuals for whom physical function oscillates and this is the reflection of cyclical or less predictable influences (4).

Decline in physical performance increases as individuals' age and it is associated with increased risk of disability especially in older women (5, 6). Older people highly value their mobility, seeing its loss as a serious disadvantage which makes this an important public health concern given the increasingly ageing population (7, 8). Physical performance tests are integrated markers of aging and current health which are influenced by several physiological and clinical characteristics and the social environment (9). These tests are consistently associated with poorer well-being and quality of life in old age, overall health status accurately predict subsequent health outcomes including multimorbidity in older people (9-11). It is worth noting that in a population of nonagenarians and non-disabled people where other risk factors lose their prognostic value, decline in physical performance is also a predictor of subsequent mortality (12, 13).

Walking speed (WS) has been recognized as an objective, useful, practical, accessible and easy to use measure in clinical and epidemiologic studies because it integrates known and unrecognized disturbances in multiple organ systems that affect survival (14, 15). It is an important element in the overall clinical assessment of elderly subjects in a similar manner to blood pressure or heart rate given its ability to measure overall physical activity and its reliability to predict future events (14-17).

The majority of older people living alone are women because of their longer disability adjusted life years compared to men and most of them need assistance in their daily life (2, 18). Therefore, identifying factors which predict physical performance and are associated to poor physical performance in middle aged women could identify high risk subpopulations and

contribute to setting up prevention and management strategies that will improve the quality of life.

Puberty marks the onset of endogeneous oestrogen exposure in women. This oestrogen stimulates female characteristics at puberty and levels fluctuate with menstrual cycles throughout women's reproductive life. There is however an important surge in oestrogen levels after puberty during pregnancies in women. This surge represents a massive exposure to oestrogens in women which increases further with repeated pregnancies. The pattern of decline in physical performance varies greatly between sexes, with women showing a greater decline in physical performance at middle age around the time of menopause compared to men (19, 20). This difference between men and women suggests that there are sex-linked dependent factors which may influence the rates of decline with age in women and the highest level of performance they can achieve (19-21). Changes in hormonal exposure such as menopause have been implicated as one of the factors responsible for this because physical performance declines at a greater rate as from midlife onwards and could be affected by changes in hormonal exposures (19-21). Women on average lose 80% of their estrogens during their first year of menopause (22) and around this same time there is an accelerated decline in physical function (3, 12, 19, 20, 23) related to this loss of estrogen (3, 20, 24). Moreover, other sex-linked dependent factors such as high parity and adolescent pregnancy have been said to influence physical function (25). The multiple accumulated demands associated with childbirth and repeated pregnancies may contribute to a decline in physical performance in women as resources used during childbirth cannot be used for later repair (26). Again, childbirth could indirectly contribute to decline in physical performance through weight gain and body mass later in life (27, 28). Studies have examined the association between menopause and physical activity, but the results have been contradictory so far. Bassey and al found that natural oestrogen or hormone replacement therapy had no effect in improving physical performance in middle-aged whereas another study found that reduction in oestrogen levels as seen in menopause was associated to decline in physical functioning (29, 30). Moreover, the effect of age in the association between menopause and physical function has not been completely examined.

Hence, as a result of the sparse evidence on the subject in this population and with WS being increasingly measured in epidemiological studies as an indicator of motor performance and its ability to predict the occurrence of events such as death or dementia; we sought to identify the determinants of WS among the reproductive characteristics of middle-aged French women.

OBJECTIVES

RESEARCH QUESTION

- What are the hormonal determinants of WS in French middle aged and elderly women?

OBJECTIVES

a) General objective

To analyze the relationship between hormonal exposure and WS in French women aged 45 years and above

b) Specific objectives

- To determine endogenous estrogens exposure from characteristics of women's reproductive history and assess its influence on WS
- To identify sources of exogenous hormonal exposure in women and assess its influence on WS
- To assess whether these different hormonal exposures are independently associated with WS

POPULATION AND METHODOLOGY

1. CONSTANCES Study

This study will use cross-sectional baseline data from the French prospective CONSTANCES ("Cohorte des Consultants des Centres d'examens de Santé"). Constances is a "general purpose" population-based national epidemiological cohort which began in 2012 and ended in 2019 and comprises of 200,000 voluntary adults aged between 18 and 69 years (31, 32). The source population is that of the people in France whose health insurance is administered by the *Caisse nationale d'assurance maladie des travailleurs salaries* (CNAMTS) and this accounts for about 85% of the French population (33). The sample is representative of France's adult population in terms of age, sex and social category. The cohort participants are included in 17 Health Screening Centers (HSCs) located in 16 different districts ("départements") in different regions of Metropolitan France (Figure 1). The HSCs which are part of the study were selected according to the distribution of risk factors and majors diseases in the general population thereby providing much heterogeneity (33). Moreover, the number of CONSTANCES subjects in each HSC varied according to the size of each HSC.

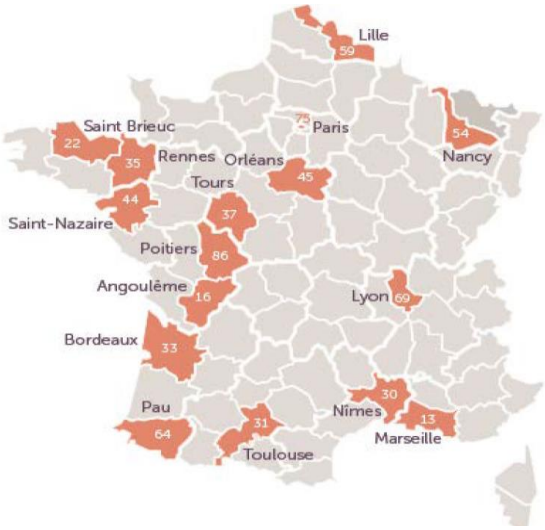


Figure 1: Geographical recruitment of the CONSTANCES Cohort (31)

Participants who consented to participate filled a written informed consent. They were then given self-administered questionnaires ("Health and Lifestyle" questionnaire, and a full "Job history") and underwent medical examination in an HSC. Biological samples were collected following the medical examination and specific tests such as physical performance tests and cognitive tests were carried out. Additional data is regularly extracted *Système national d'information inter-régimes de l'Assurance maladie* (SNIIRAM) and *Caisse Nationale d'Assurance Vieillesse* (CNAV) databases and linked to each individual in addition to the annual self-administered follow-up questionnaires (33).

2. Study population

Our study included women aged above 45 years from CONSTANCES recruited during the study period. Age was limited to 45 years because physical performances tests were only performed in CONSTANCES from the age of 45 (33). All women who filled the Women's Health questionnaire were included in our study. We excluded women who did not have any

information on our exposures of interest despite filling the questionnaire, any woman who presented conditions that could abnormally modify their WS (pregnancy, post-partum, fractures during the year preceding their enrollment, Parkinson's disease) and those without data on WS test. HSCs were assessed and periods during which a neurophysiologist had not yet been hired making the centres not fully operational were excluded.

3. Hormonal exposure and other covariates

a) Exposure variables

Characteristics of reproductive life such as menopausal status, age at menopause, type of menopause, age at menarche, parity, hormonal contraceptives and use of post-menopausal therapy were self-reported by women in a specific questionnaire.

i. Markers of endogenous estrogens exposure

Endogenous estrogens exposure was assessed through characteristics of reproductive life with the following variables being defined for all women:

- **Age at menarche**: it was the age during the first menstrual period.
- **Nulliparous**: it was defined as having no child during the life.
- **Parity**: it was defined as the total number of live births.
- **Age at first pregnancy**: this was defined as the age during the first live birth.
- **Menopausal status:** it was defined as cessation of menstrual periods for more than 12 months or bilateral oophorectomy or use of postmenopausal hormone therapy (HT) which ever occurred first. In cases where this information was not self-reported, women were considered as menopaused if they self-reported menopause without any other information or were older than 60 years old or had undergone a hysterectomy or were artificially menopaused by chemotherapy for cancer. Women were considered as non-menopaused if they reported giving birth within the last 12 months before enrollment, were breastfeeding, were using fertility treatment or contraception or presented with a pathology related to reproductive life especially endometriosis. Women who reported pre/perimenopause were considered as non-menopaused. The remaining women were considered as non-classified.

Other variables were defined only among postmenopausal women

- **Age of menopause**: this was the age at which the women had been classified as menopaused as described above.
- **Type of menopause:** it was classified as artificial if menopause had occurred after bilateral oophorectomy, hysterectomy or after chemotherapy and natural otherwise.
- **Time since onset of menopause:** This was estimated as the time between age at menopause and age at inclusion.

- **Duration of reproductive life span**: this was estimated as the time between age at menarche and age at menopause.

ii. Exogeneous exposure

- **Hormonal contraception**: it was defined as each hormonal treatment used to prevent pregnancies classified as contraceptive pills (combined oral contraceptive pills, progesterone only pills) and it was defined for all women.
- **HT**: this was defined as use of estrogens (oral or transdermal) after menopause, alone or combined with progestogens and defined only for postmenopausal women.

b) Covariates

Body Mass Index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Education represented the number of years in school and monthly revenues were assessed and reported. Physical activity was self-reported in a questionnaire through a 6 parameters scale ranging from not active at all outside of work to very active outside of work. Smoking status was defined as never, past or current and alcohol as no, moderate or unsafe consumption. Hypertension was defined according to the World Health Organization criteria (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of antihypertensive drugs), hypercholesterolemia by low density lipoprotein ≥4.14 mmol/L or use of cholesterol-lowering drugs, and diabetes by fasting blood glucose level ≥7 mmol/L or use of antidiabetic drugs. Depression was evaluated using the Centre for Epidemiological Studies-Depression Scale (CES-D) based on a cutoff of ≥16 or use of specific medications or therapy and cognitive functions was assessed using the mini-mental state examination (MMSE). Cardiovascular affections were defined as a past history of either angina or myocardial infarction or stroke or arteritis of the lower limbs. Respiratory affections were defined as a chronic bronchitis or emphysema or asthma. Renal affections were chronic kidney disease or any other renal impairment. Arthritis was self-reported in the questionnaire and cancer of the uterus or ovaries was measured as any woman who reported a cancer of the uterus and/or ovaries or who was receiving treatment for any of the aforementioned cancers.

4. Outcome variable

The WS test was carried out two times over a distance of 3 metres using photoelectric cells which were connected to a chronometer. Participants were first asked to walk at their usual pace and to walk a second time at a faster pace but without running, starting walking three meters before the start line and stopping after the finish line. WS was computed as the distance divided by the duration and expressed as cm/s. Based on previous data that has shown a

greater variability in fast WS than in usual WS, the WS used in this study referred to the fast WS (34, 35).

5. Statistical analysis

a) Description of study population

Age was classified into 5 groups ([45-50[, [50-55[, [55-60[, [60-65[, ≥65), and height was studied in centimetres and classified into 4 groups (<157, [157-161[, [161-166[, ≥166). BMI was classified into 3 groups according to the World Health Organisation classification: <25, [25-30[, ≥30. Monthly revenues were categorized into 3 ranges according to the tertiles ([45€ -1500€[, [1500€ - 2180€[, ≥2180€). Marital status was classified into 3 groups (in a relationship, single, separated/divorced/widow) whereas education was classified into 4 groups as follows: no education/primary education, high school degree, bachelor's degree, master's Degree/PhD/Others. Physical activity was classified into 3 groups (inactive, moderately active and very active) as well as alcohol consumption (no consumption, moderate consumption and unsafe consumption) and smoking status (never, past, current). MMSE were classified into tertiles (≥29, 28 and <28). Hypercholesterolemia, hypertension, diabetes, depression, respiratory affections, renal affections, cardiovascular affections, arthritis and cancer of the ovaries and uterus were all classified into 2 groups (no, yes).

WS was estimated for each category of baseline characteristics and compared using T tests or analysis of variance (ANOVA) before and after adjustment for age.

The association between the baseline characteristics and the exposure variables (age at menarche, parity, age at first pregnancy, menopausal status, type of menopause, age at menopause, time since onset of menopause, duration of reproductive life span, oral contraceptive pills use and HT) was assessed using chi-square tests before and after adjustment for age.

b) Linear association of hormonal exposure with WS

The association of WS with exposure variables was firstly assessed using linear mixed models to account for the within-centre correlation for each of the exposures. Analyses were done among all women and specifically among postmenopausal women.

Age at menarche was used as a continuous variable and as a categorical into 4 classes (<12,]12-13],]13-14], >14 years). Nulliparous was used as no (women with at least one child) and yes (nulliparous women). Parity and age at first pregnancy were used as continuous variables for one unit increase. Menopause was classified in 3 groups as Yes, No and the not classified group was excluded. Age at menopause was used as a continuous variable for a 5-year increase and was also classified into premature (<40 years), early ([40-45[years), normal ([45-55] years) and late (>55 years) and further into premature/not premature. Type of

menopause was categorized as natural or artificial. We also created a variable which combined age at menopause (premature or not premature) and type of menopause (natural or artificial). Time since onset of menopause and duration of reproductive life span were used as continuous variables for a 5-year increase. Oral contraceptive pills use was classified in 3 groups for all women (never, past, current) and 2 groups for menopaused women (never, ever) and HT into 3 groups (never, past, current).

The first model was adjusted on age as continuous variable and centre (as a random effect). The second model was then further adjusted for potential confounders (height, BMI, marital status, revenues, education, physical activity, alcohol, smoking, cancer of ovaries and/or uterus, respiratory affections and renal affections). These variables were selected among variables that were associated to WS or at least one of the exposure variables after adjusting on age without being suspected to mediate the association of hormonal exposure with WS (36). The third model was a multiadjusted model which included all the variables which were statistically significant in the second model after assessing that there was no significant interactions between different hormonal exposures on WS. Lastly, the fourth model was made of significant variables from the third model and further adjusted for potential mediating factors (hypertension, diabetes, hypercholesterolemia, cardiovascular affections, depression, MMSE). For each adjustment covariate, we created an additional category for missing values.

c) Multinomial logistic regression of hormonal exposure with WS

The odds ratio and 95% confidence intervals of the association of WS with exposure variables were secondly assessed by a multinomial logistic regression using the highest quartiles of WS as reference. This analysis was carried out to test the hypothesis that the potential effect of our exposure variables is not the same depending on which quartile of WS individuals belong to.

All the exposure variables were used as categorical variables and the categories for age at menarche, nulliparous, age at menopause, type of menopause, oral contraceptives pills and HT were those described above. Parity was classified into 4 categories (no child, 1 child, 2 children, 3 or more children). Age at first pregnancy was categorized as <24, [24-27[, [27-30[, and ≥30 years. Time since onset of menopause in years was classified in 4 groups in menopaused women (≤4.5,]4.5-9.5],]9.5-14], >14 years) and duration of reproductive life span in years was classified into 4 categories (<35, [35-38[, [38-41[, ≥41 years).

The models were the same as those used in the linear regression analyses.

Analysis were carried out using the SAS software version 9.4 (SAS Institute, Cary, NC) and p-values <0.05 were considered statistically significant.

RESULTS

1. Study population

There were 99701 subjects aged ≥45 years in the CONSTANCES study. First, we excluded subjects recruited when centres were not fully operational (n=37967), men (n=29336) and women without exposure data (n=973). Of the 31425 remaining women, we excluded those who presented conditions that could modified WS: pregnancy (n=28), immediate post-partum (n=10), compression or hip fractures in the year preceding enrollment (n=13) and Parkinson's disease (n=51). After exclusion of women without WS data (n=6766), the final sample consisted of 24557 women aged ≥ 45 years as seen in Figure 2.

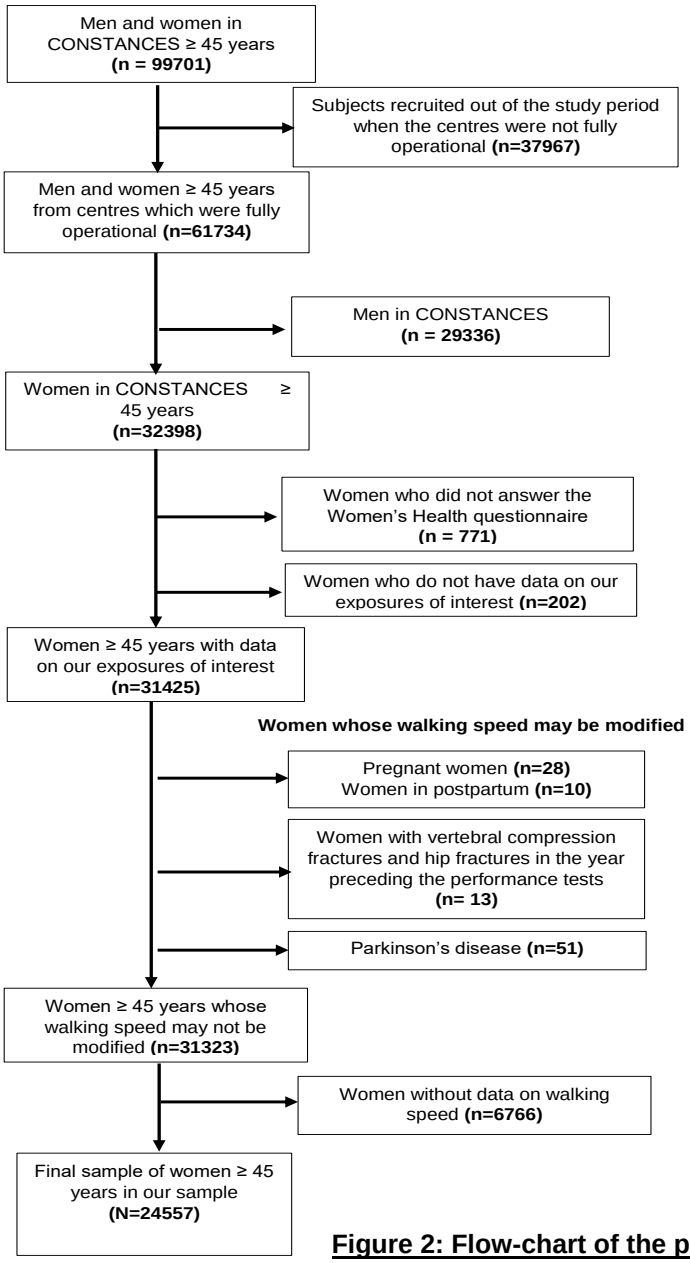


Figure 2: Flow-chart of the population selection

Women without WS data were younger (57.1 vs 57.5, p<0.010), mostly single (18.9% vs 14.0%, p<0.001), more educated (20.5% vs 15.7%, p<0.001) and presented a higher BMI (25.1 vs 24.9, p=0.026) than included women. However, there was no difference in number of children (2.19 vs 2.20, p=0.242) age at menopause between both groups (50.2 vs 50.4, p=0.081).

2. Characteristics associated to WS

WS was normally distributed as seen in Figure 3. The mean WS was 173.1 cm/s and ranged from 33cm/s to 300 cm/s.

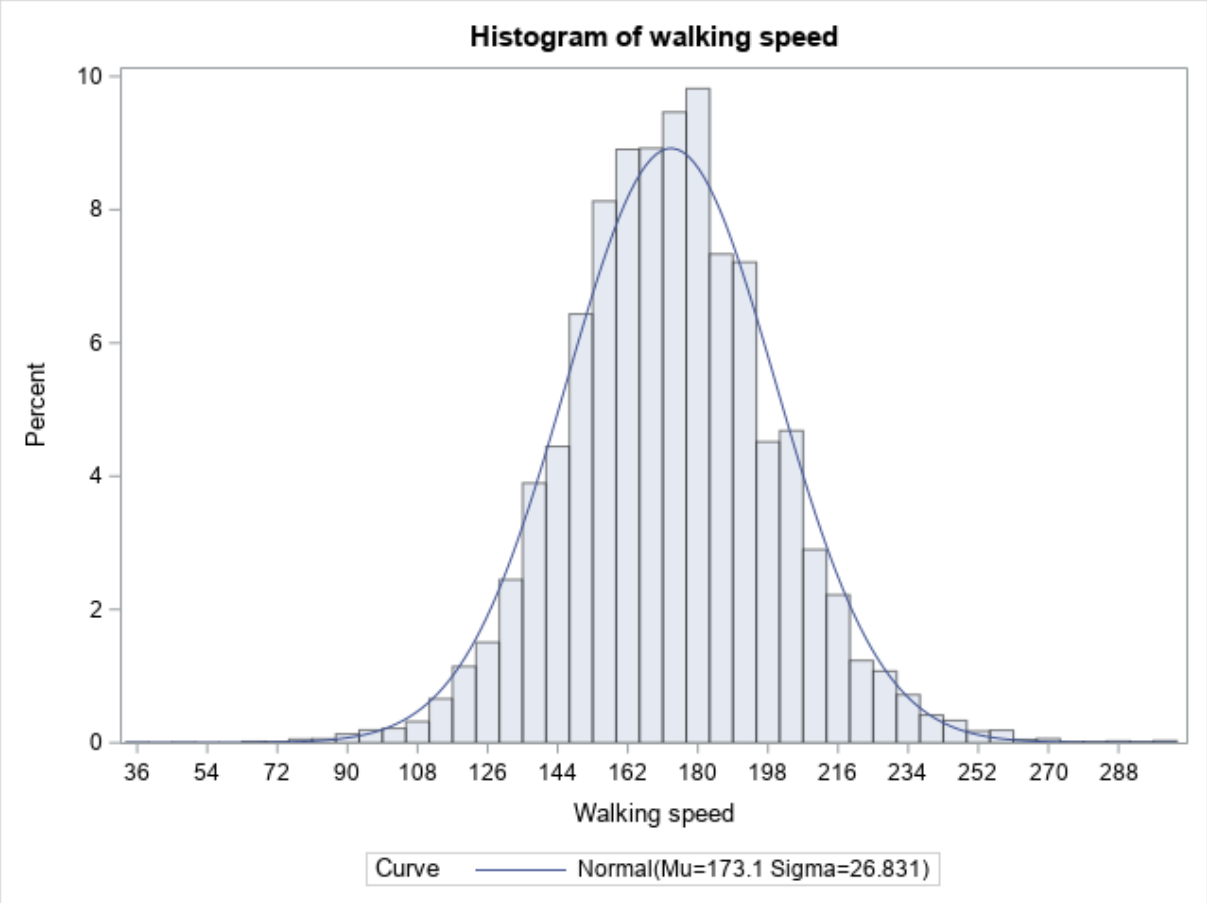


Figure 3: Histogram of walking speed

All baseline characteristics except cancer of the ovaries and/or uterus were associated to WS after adjusting for age as seen in Table I. Mean age was 57.5 years. Women who presented the lower WS were more likely than the others to be older, shorter, overweight, less educated and to suffer from cardiovascular disease and neurological disorders.

Table I: Baseline characteristics and their association with walking speed

Characteristics		N (%)	Walking speed (cm/s) Mean (SD)	p value	p* value
N (%)		24557 (100.0)	173.1 (26.8)		
Age yr					
	[45-50[	4577 (18.6)	181.0 (25.9)		
	[50-55[	4907 (20.0)	178.2 (26.4)		
	[55-60[	5130 (20.9)	174.1 (25.8)	<0.001	
	[60-65[	4917 (20.0)	169.9 (26.1)		
	≥65	5026 (20.5)	163.1 (26.3)		
Height cm (MV=763)					
	<157	4697 (19.7)	163.7 (26.4)		
	[157-161[	6951 (29.3)	170.6 (25.8)	<0.001	<0.001
	[161-166[	5830 (24.5)	175.7 (26.5)		
	166	6316 (26.5)	180.2 (25.9)		
BMI kg/m² (MV=1017)					
	< 25	13985 (59.4)	177.9 (25.8)		
	25 - 30	6423 (27.3)	168.9 (25.9)	<0.001	<0.001
	≥30	3132 (13.3)	160.2 (27.4)		
Marital status (MV=568)					
	In a relationship	15242 (63.5)	173.4 (26.9)		
	Single	3358 (14.0)	176.1 (26.4)	<0.001	<0.001
	Separated/Divorced/Widow	5389 (22.5)	170.8 (26.4)		
Revenues (MV=2282)					
	<45€ - <1500€	2271 (10.2)	163.8 (28.9)		
	1500€ - <2180€	6459 (29.0)	168.8 (26.8)	<0.001	<0.001
	2180€ - 4200€ +	13545 (60.8)	177.4 (25.5)		
Education (MV=462)					
	No education/Primary education	7326 (30.4)	162.2 (26.2)		
	High school degree	4291 (17.8)	171.7 (26.0)	<0.001	<0.001
	Bachelor's degree	8686 (36.1)	178.9 (24.9)		
	Master's Degree/PhD/Others	3792 (15.7)	183.1 (25.3)		
Physical activity (MV=1272)					
	Inactive	5009 (21.5)	169.8 (27.5)		
	Moderately active	10325 (44.3)	174.2 (26.7)	<0.001	<0.001
	Very active	7951 (34.2)	175.3 (25.9)		
Alcohol consumption (MV=3486)					
	No consumption	3837 (18.2)	170.3 (27.3)		
	Moderate consumption	15407 (73.1)	174.9 (26.1)	<0.001	<0.001
	Unsafe consumption	1827 (8.7)	175.9 (26.9)		
Smoking status (MV=1146)					
	Never	12001 (51.3)	172.0 (27.4)		
	Past	3138 (13.4)	174.2 (26.7)	<0.001	<0.001
	Current	8272 (35.3)	174.4 (25.9)		
Hypercholesterolemia (MV=15)					
	No	15963 (65.0)	175.3 (26.8)	<0.001	<0.001
	Yes	8579 (35.0)	169.0 (26.3)		
Hypertension (MV=15)					
	No	16616 (67.7)	175.7 (26.1)	<0.001	<0.001
	Yes	7926 (32.3)	167.7 (27.6)		
Diabetes					
	No	24052 (97.9)	173.5 (26.6)	<0.001	<0.001
	Yes	505 (2.1)	156.1 (30.1)		
Depression (MV=327)					
	No	18392 (75.9)	174.1 (26.4)	<0.001	<0.001
	Yes	5838 (24.1)	170.1 (27.8)		
MMSE (MV=140)					
	≥29	12960 (53.1)	177.0 (25.6)		
	28	4651 (19.1)	172.7 (27.3)	<0.001	<0.001
	<28	6806 (27.8)	166.0 (27.3)		

Table I: follows

Characteristics	N (%)	Walking speed (cm/s) Mean (SD)	p value	p* value
Respiratory affections (MV=332)				
No	22028 (90.9)	173.4 (26.7)	<0.001	<0.001
Yes	2197 (9.1)	170.3 (27.8)		
Renal affections (MV=376)				
No	24089 (99.6)	173.1 (26.8)		<0.001
Yes	92 (0.4)	175.2 (30.1)		
Cardiovascular affections (MV=346)				
No	23775 (98.2)	173.4 (26.8)	<0.001	<0.001
Yes	436 (1.8)	160.5 (27.8)		
Arthritis (MV=629)				
No	23499 (98.2)	173.4 (26.7)	<0.001	<0.001
Yes	429 (1.8)	163.7 (29.6)		
Cancer of ovaries and uterus				
No	24244 (98.7)	173.1 (26.8)	0.303	0.685
Yes	313 (1.3)	171.5 (27.1)		

MV : missing values
BMI : body mass index
*** : adjusted for age**

The Table II shows the WS according to the different reproductive life characteristics. Among all women, those who had their menarche after 14 years, had more than 3 children, gave birth to their first child after 30 years, were not menopaused and were ever users of contraceptive presented a faster WS as compared to the others. In addition, women who were menopaused naturally, between the ages of 45 and 55 years and who were ever users of HT had a faster WS than other menopaused women. Parity was inversely correlated to age at first pregnancy ($r= -0.28$, $p<0.001$) and artificially menopaused women were menopaused at a younger age. Finally, WS decreased with increased time since menopause and WS was the fastest for women who presented a duration of reproductive life span between 35 and 38 years.

Table II: Reproductive characteristics and walking speed

Characteristics		Total	Walking speed (cm/s) Mean (SD)	P value
N				
Age menarche, yr (MV=1220)				
	Mean (SD)	13.0 (1.7)		
Age menarche (MV=1220)				
	≤12	9484 (40.6)	171.3 (26.5)	
	]12-13]	5518 (23.6)	174.4 (26.2)	<0.001
	]13-14]	4511 (19.4)	175.1 (26.8)	
	> 14	3824 (16.4)	174.9 (27.6)	
Nulliparous (MV=1476)				
	No	2184 (9.5)	175.3 (26.8)	<0.001
	Yes	20897 (90.5)	172.9 (26.8)	
Parity (MV=1476)				
	Mean (SD)	1.9 (1.1)		
Parity (MV=1476)				
	0	2184 (9.5)	175.3 (26.8)	
	1	4139 (17.9)	171.3 (26.2)	<0.001
	2	10296 (44.6)	172.8 (26.1)	
	≥3	6462 (28.0)	174.4 (28.2)	
Age at first pregnancy (MV=98)*				
	Mean (SD)	26.7 (4.9)		
Age at first pregnancy (MV=98)*				
	<24 years	5614 (27.0)	164.9 (26.9)	
	[24-27[years	5367 (25.8)	173.2 (26.4)	<0.001
	[27-30[years	4507 (21.7)	176.9 (26.1)	
	≥30years	5311 (25.5)	178.1 (25.6)	
Menopause				
	No	5999 (24.4)	180.9 (25.6)	
	Yes	18511 (75.4)	170.6 (26.7)	<0.001
	Not classified	47 (0.2)	164.6 (31.8)	
Type of menopause **				
	Natural	15969 (86.3)	171.1 (26.8)	<0.001
	Artificial	2542 (13.7)	167.5 (26.3)	
Age of menopause (MV=669)**				
	Mean (SD)	50.4 (5.0)		
Age of menopause (MV=669)**				
	< 40	544 (3.1)	166.0 (27.0)	
	[40-45[	1359 (7.6)	169.4 (28.5)	<0.001
	[45-56[	13907 (77.9)	171.5 (26.4)	
	≥56	2032 (11.4)	166.7 (26.7)	
Time since onset of menopause (MV=669)**				
	≤4.5	4507 (25.3)	176.8 (26.1)	
	]4.5-9.5]	4302 (24.1)	171.9 (25.8)	<0.001
	]9.5-14]	4655 (26.1)	169.0 (2.7)	
	>14	4378 (24.5)	164.6 (26.4)	
Duration of reproductive life span in years (MV=1550)**				
	Mean (SD)	37.4 (5.1)		
Duration of reproductive life span in years (MV=1550)**				
	< 35	4016 (23.7)	170.4 (27.5)	
	[35-38[	3865 (22.8)	172.2 (26.1)	<0.001
	[38-41[	4788 (28.2)	171.8 (26.2)	
	≥41	4292 (25.3)	168.9 (26.3)	
Use of contraceptive pills (MV=1497)				
Never		2499 (10.8)	168.3 (28.4)	
Ever		20561 (89.2)	174.4 (26.3)	<0.001
	Past	19879 (86.2)	174.2 (26.3)	
	Current	682 (3.0)	180.8 (25.0)	
Post-menopausal hormonal therapy (MV=791)**				
Never		15068 (85.0)	170.3 (26.6)	
Ever		2652 (15.0)	174.1 (26.2)	<0.001
	Past	365 (2.1)	168.4 (25.9)	
	Current	2287 (12.9)	175.0 (26.1)	

***: in parturient women only (n=20896)**
****: In menopaused women only (n=18511)**

3. Characteristics associated to exposure variables

The table III shows the association of general characteristics of women with menopausal status. After adjustment for age, menopaused women were shorter, less educated and presented worse cardiovascular and neurological profiles than no menopaused women. As expected, they were also more likely to have had a cancer of ovaries and/or uterus.

The associations of general characteristics of women with other hormonal exposures (age at menarche, parity, age at first pregnancy, type of menopause, age at menopause, time since onset of menopause, duration of reproductive life span, oral contraceptive pills and post-menopausal hormonal therapy) are available in the Appendices section (Appendix 2, 3, 4, 5, 6, 7, 8, 9 and 10 respectively) and summarized in the Table IV.

Table III: Baseline characteristics and their association with menopause

Characteristics		Menopausal status		p value	p* value
		No	Yes		
N (%)		5999 (24.5)	18511 (75.5)		
Age yr					
	[45-50[	3776 (62.9)	787 (4.3)		
	[50-55[	2028 (33.8)	2860 (15.5)		
	[55-60[	195 (3.3)	4921 (26.6)	<0.001	
	[60-65[	0 (0.0)	4917 (26.6)		
	≥ 65	0 (0.0)	5026 (27.0)		
Height cm (MV=762)					
	<157	697 (12.0)	3993 (22.3)		
	[157-161[	1466 (25.3)	5473 (30.5)	<0.001	0.003
	[161-166[	1538 (26.5)	4277 (23.8)		
	≥166	2104 (36.2)	4200 (23.4)		
BMI kg/m² (MV=1016)					
	< 25	3693 (64.3)	10269 (57.9)		
	25 - 30	1349 (23.5)	5060 (28.5)	<0.001	0.483
	≥ 30	705 (12.2)	2418 (13.6)		
Marital status (MV=567)					
	In a relationship	3693 (63.0)	11531 (63.8)		
	Single	1109 (18.9)	2235 (12.3)	<0.001	0.186
	Separated/Divorced/Widow	1059 (18.1)	4316 (23.9)		
Revenues (MV=2279)					
	<45€ - <1500€	503 (9.0)	1753 (10.5)		
	1500€ - <2180€	1330 (24.0)	5114 (30.7)	<0.001	<0.001
	2180€ - 4200€ +	3721 (67.0)	9810 (58.8)		
Education (MV=461)					
	No education/Primary education	1200 (20.3)	6104 (33.6)		
	High school degree	973 (16.5)	3311 (18.3)	<0.001	<0.001
	Bachelor's degree	2476 (41.9)	6195 (34.1)		
	Master's Degree/PhD/Others	1256 (21.3)	2534 (14.0)		
Physical activity (MV=1271)					
	Inactive	1569 (27.0)	3423 (19.6)		
	Moderately active	2797 (48.2)	7509 (43.1)	<0.001	0.542
	Very active	1441 (24.8)	6500 (37.3)		
Alcohol consumption (MV=3473)					
	No consumption	994 (19.0)	2830 (17.9)		
	Moderate consumption	3861 (73.8)	11526 (72.9)	<0.001	0.426
	Unsafe consumption	380 (7.2)	1446 (9.2)		
Smoking status (MV=1139)					
	Never	2779 (48.4)	9195 (52.2)		
	Past	993 (17.3)	2138 (12.1)	<0.001	<0.001
	Current	1976 (34.4)	6290 (35.7)		

Table III: follows.

Characteristics		Menopausal status		p value	p* value
		No	Yes		
Diabetes					
	No	5946 (99.1)	18062 (97.6)	<0.001	0.052
	Yes	53 (0.9)	449 (2.4)		
Hypertension (MV=15)					
	No	4936 (82.3)	11646 (63.0)	<0.001	0.205
	Yes	1062 (17.7)	6851 (37.0)		
Hypercholesterolemia (MV=15)					
	No	5021 (83.7)	10907 (59.0)	<0.001	<0.001
	Yes	977 (16.3)	7590 (41.0)		
Depression (MV=327)					
	No	4664 (78.8)	13693 (75.0)	<0.001	<0.001
	Yes	1254 (21.2)	4572 (25.0)		
MMSE (MV=140)					
	≥29	3468 (58.1)	9476 (51.5)		
	28	1060 (17.8)	3582 (19.4)	<0.001	<0.001
	<28	1438 (24.1)	5346 (29.1)		
Respiratory affections (MV=332)					
	No	5341 (90.2)	16644 (91.2)	0.032	0.719
	Yes	578 (9.8)	1615 (8.8)		
Renal affections (MV=375)					
	No	5906 (99.8)	18137 (99.6)	0.010	0.016
	Yes	12 (0.2)	80 (0.4)		
Cardiovascular affections (MV=346)					
	No	5874 (99.2)	17854 (97.9)	<0.001	0.044
	Yes	48 (0.8)	388 (2.1)		
Arthritis (MV=629)					
	No	5786 (98.7)	17669 (98.1)	0.003	0.088
	Yes	78 (1.3)	348 (1.9)		
Cancer of ovaries and uterus					
	No	5966 (99.4)	18232 (98.5)	<0.001	<0.001
	Yes	33 (0.6)	279 (1.5)		

MV : missing values
BMI : body mass index
*** : adjusted for age**

4. Association of hormonal exposures and WS

a. Linear regression

Table V shows the association of hormonal exposures and WS in all women using linear mixed models. After adjustment for age and center, there was a significant association of WS with age at menarche (β for 1-yr increase=0.68; 95%CI: 0.48; 0.87, p<0.001), that was partially attenuated after adjustment for confounders (β for 1-yr increase=0.35; 95% CI: 0.16; 0.53, p<0.001). In addition, WS increased with number of children (β per child=0.34; 95% CI: 0.04; 0.65, p=0.027 and β per child=0.35; 95% CI: 0.04; 0.65, p<0.025, in model 1 and model 2, respectively) and with age at the first pregnancy (β for 1-yr increase=0.61; 95% CI: 0.54; 0.68, p<0.001 and β for 1-yr increase=0.19; 95% CI: 0.12; 0.26, p<0.001, in model 1 and model 2, respectively). By contrast, WS was not associated with menopausal status and contraceptive use after adjustment for age, center and potential confounders.

In a multiadjusted model (model 3), we found independent associations of WS with age at menarche, parity and age at first pregnancy (β for 1-yr increase=0.34; 95% CI: 0.15; 0.53, p<0.001, β per child=0.84; 95% CI: 0.45; 1.24, p<0.001, β for 1-yr increase=0.24; 95% CI: 0.16; 0.32, p<0.001, for age at menarche, parity and age at first pregnancy, respectively). These differences in 0.35 cm/s, 0.84 cm/s and 0.24 cm/s observed are equivalent to be 4 months, 5 months and 3 months younger, respectively. Adjustment for several cardiovascular risk factors, cognitive function and depression did not change the results (model 4).

Table VI shows the association of hormonal exposures and WS in menopaused women. As observed among all women, there was a significant association of WS with age at menarche (β for 1-yr increase=0.65; 95%CI: 0.42; 0.87, p<0.001 and β for 1-yr increase=0.35; 95% CI: 0.14; 0.57, p=0.001, in model 1 and 2, respectively). Similarly, in models 2, we found that WS increased with the number of children and the age at first pregnancy (Model 2: β per child=0.42; 95% CI: 0.07; 0.77, p<0.001 and β for 1-yr increase =0.17; 95% CI: 0.08; 0.25, p<0.001). Regarding the specific characteristics of postmenopausal women, WS increases with age at menopause (Model2 : β for 5-yr increase=0.46; 95%CI: 0.11; 0.82, p=0.010) and was lower among women with artificial menopause (Model 2: β=-2.45; 95%CI: -4.45; -0.44, p=0.016). When age at menopause (premature/no premature) and type of menopause (natural/artificial) were combined, we identified that women who presented artificial or premature menopause walked slower than others. Nevertheless, the effect size of premature menopause could be attenuated among women with artificial menopause (figure 3). Finally, time since menopause was inversely associated with WS (Model 2: β for 5-yr increase=-0.47; 95%CI: -0.82; -0.11, p=0.010) but duration of reproductive life span did not influence it.

In a multiadjusted model (model 3), premature menopause, artificial menopause and time since menopause were no longer significant. However, there were significant and independent associations of WS with age at menarche (β for 1-yr increase=0.36; 95%CI: 0.14; 0.57, p<0.001), parity (β per child=0.71; 95%CI: 0.26; 1.17, p=0.002) and age at the first birth (β for 1-yr increase=0.19; 95%CI: 0.10; 0.28, p<0.001). The increase in 0.36 cm/s, 0.71 cm/s and 0.19cm/s are equivalent to be 5 months, 10 months and 2.5 months younger, respectively. Further adjustment for cardiovascular risk factors, depression and cognitive function did not modify the results.

Table IV: Cross-sectional association between reproductive life characteristics and walking speed in all women

Characteristics of reproductive life	Walking speed (cm/s)							
	Model 1 (n=24557)			Model 2 (n=24557)		Model 3 (n=21925)		Model 4 (n=21925)	
	N	Beta (95%CI)	p	Beta (95%CI)	p	Beta (95%CI)	p	Beta (95%CI)	p
Age at menarche									
For 1-year increase	23337	0.68 (0.48; 0.87)	<0.001	0.35 (0.16; 0.53)	<0.001	0.34 (0.15 ; 0.53)	0.001	0.34 (0.15 ; 0.53)	<0.001
≤12 years	9484	Reference		Reference					
]12-13] years	5518	2.17 (1.32; 3.02)	<0.001	0.43 (-0.37; 1.23)	0.289				
]13-14] years	4511	3.17 (2.26; 4.08)	<0.001	1.59 (0.73; 2.44)	<0.001				
> 14 years	3824	2.40 (1.44; 3.36)	<0.001	1.23 (0.32; 2.14)	0.009				
p for linear trend [#]			<0.001		<0.001				
Nulliparous									
No	20897	Reference		Reference		Reference		Reference	
Yes	2184	-0.23 (-1.34; 0.88)	0.689	-0.18 (-1.33; 0.98)	0.762	0.00 (-1.31;1.31)	0.999	0.02 (-1.29;1.33)	0.974
Parity									
Per child	23081	0.34 (0.04; 0.65)	0.027	0.35 (0.04; 0.65)	0.025	0.84 (0.45; 1.24)	<0.001	0.85 (0.45; 1.24)	<0.001
Age at first pregnancy									
For 1-year increase	20792	0.61 (0.54; 0.68)	<0.001	0.19 (0.12; 0.26)	<0.001	0.24 (0.16; 0.32)	<0.001	0.22 (0.14; 0.30)	<0.001
Menopause									
No	5999	Reference		Reference					
Yes	18511	-0.48 (-1.55; 0.60)	0.358	0.54 (-0.47; 1.55)	0.272				
Use of contraceptive pills									
Never	2499	Reference		Reference					
Past	19879	3.31 (2.21; 4.38)	<0.001	0.70 (-0.33; 1.74)	0.178				
Current	682	4.36 (1.09; 5.64)	0.005	0.00 (-2.14; 2.14)	0.999				
p ANOVA			<0.001		0.310				

[#] using the median of each class

Model 1: adjusted for age and centre

Model 2: model 1 + height, BMI, marital status, revenues, education, physical activity, alcohol, smoking status, cancer of the ovaries and/or uterus, renal affections, respiratory affections

Model 3: multiadjusted using significant variables in model 2 (+ nulliparous)

Model 4: significant variables in the model 3 (+ nulliparous) + diabetes, hypertension, hypercholesterolemia, cardiovascular affections, depression, MMSE

Models 3 and 4: Parity was centred on 2.2 (average number of children among parturient women) and age at first pregnancy was centred on 26.8 years (mean age at the first pregnancy).

Table V: Cross-sectional association between reproductive life characteristics and walking speed in menopaused women

Characteristics of reproductive life	Walking speed (cm/s)								
		Model 1 (n=18511)		Model 2 (n=18511)		Model 3 (n=16410)		Model 4 (n=16410)	
	N	Beta (95%CI)	p	Beta (95%CI)	p	Beta (95%CI)	p	Beta (95%CI)	p
Age at menarche									
For 1-year increase	17553	0.65 (0.42; 0.87)	<0.001	0.35 (0.14; 0.57)	0.001	0.36 (0.14; 0.57)	<0.001	0.37 (0.14; 0.59)	0.001
≤12 years	7324	Reference		Reference					
]12-13] years	4109	2.52 (1.54;3.50)	<0.001	0.79 (-0.13; 1.71)	0.092				
]13-14] years	3338	2.83 (1.78; 3.88)	<0.001	1.41 (0.43; 2.40)	0.006				
> 14 years	2782	2.36 (1.24; 3.49)	<0.001	1.33 (0.27; 2.39)	0.015				
P for linear trend			<0.001		0.001				
Nulliparous									
No	15696	Reference		Reference		Reference		Reference	
Yes	1680	-0.11 (-1.40; 1.19)	0.869	-0.98 (-2.33; 0.36)	0.151	-0.89 (-2.44; 0.66)	0.239	-0.87 (-2.43; 0.67)	0.246
Parity									
Per child	17326	0.21 (-0.13; 0.57)	0.23	0.42 (0.07; 0.77)	<0.001	0.71 (0.26; 1.17)	0.002	0.73 (0.27; 1.18)	0.002
Age at first pregnancy									
For 1-year increase	15611	0.63 (0.55; 0.72)	<0.001	0.17 (0.08; 0.25)	<0.001	0.19 (0.10; 0.28)	<0.001	0.18 (0.09; 0.27)	0.001
Age at menopause									
For 5 years increase	17842	1.24 (0.86; 1.62)	<0.001	0.46 (0.11; 0.82)	0.010				
Premature menopause	544	-5.25 (-7.46; -3.04)	<0.001	-2.26 (-4.63; -0.49)	0.017				
Early menopause	1359	-2.81 (-4.25; -1.37)	0.003	-0.65 (-1.99; 0.70)	0.338				
Normal menopause	13907	Reference		Reference					
Late menopause	2032	-0.67 (-1.91; 0.57)	0.283	-0.48 (-1.63; 0.68)	0.409				
***p for linear trend**[#]*			<0.001		0.127				
Premature menopause	544	-4.95 (-7.09; -2.81)	<0.001	-2.45 (-4.45; -0.44)	0.016	-1.59 (-4.20; 1.02)	0.233		
No premature menopause	17298	Reference		Reference		Reference			
Type of menopause									
Natural	15969	Reference		Reference		Reference			
Artificial	2542	-3.05 (-4.20; -1.89)	<0.001	-1.32 (-2.41; -0.23)	0.021	-0.77 (-2.01; 0.47)	0.579		
Time since onset of menopause									
For 5-year since menopause	17542	-1.24 (-1.62; -0.86)	<0.001	-0.47 (-0.82; -0.11)	0.010	-0.10 (-0.56; 0.37)	0.685		

Table V: follows

Characteristics of reproductive life	Walking speed (cm/s)							
		Model 1 (n=18511)		Model 2 (n=18511)		Model 3 (n=16410)		Model 4 (n=16410)	
	N	Beta (95%CI)	p	Beta (95%CI)	p	Beta (95%CI)	p	Beta (95%CI)	p
Duration of reproductive life span									
For 5-year of duration	4016	0.70 (0.33; 1.08)	<0.001	0.21 (-0.15; 0.56)	0.253				
Post-menopausal hormonal therapy									
Never	15068	Reference		Reference					
Past	365	-0.21 (-2.93; 2.49)	0.871	-1.62 (-4.15; 0.90)	0.198				
Current	2287	2.85 (1.70; 4.00)	<0.001	0.22 (-0.85; 1.30)	0.674				
P for ANOVA			<0.001		0.383				
Use of contraceptive pills									
Never	2160	Reference		Reference					
Ever	14949	3.10 (1.86; 4.35)	<0.001	0.52 (-0.66; 1.70)	0.366				

[#] using the median of each class

Model 1: adjusted for age and centre

Model 2: model 1 + height, BMI, marital status, revenues, education, physical activity, alcohol, smoking status, cancer of the ovaries and/or uterus, renal affections, respiratory affections

Model 3: multiadjusted using significant variables in model 2 (+ nulliparous)

Model 4: significant variables in the model 3 (+ nulliparous) + diabetes, hypertension, hypercholesterolemia, cardiovascular affections, depression, MMSE

Models 3 and 4: Parity was centred on 2.2 (average number of children among parturient menopaused women) and age at first pregnancy was centred on 26.3 years (mean age at the first pregnancy among menopaused women).

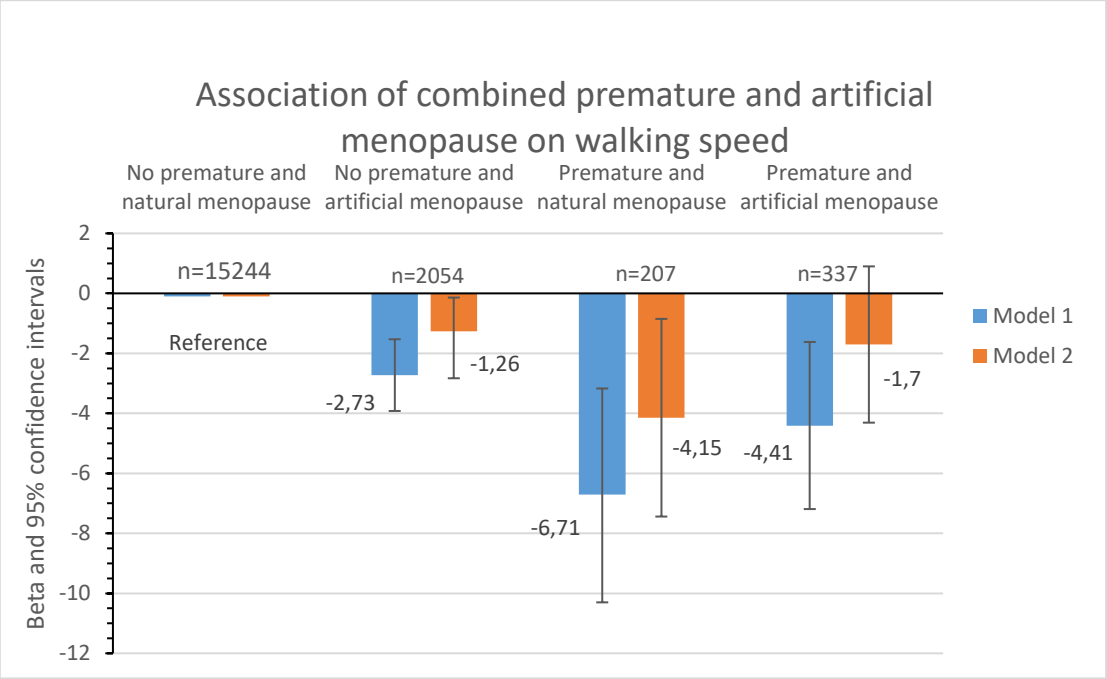


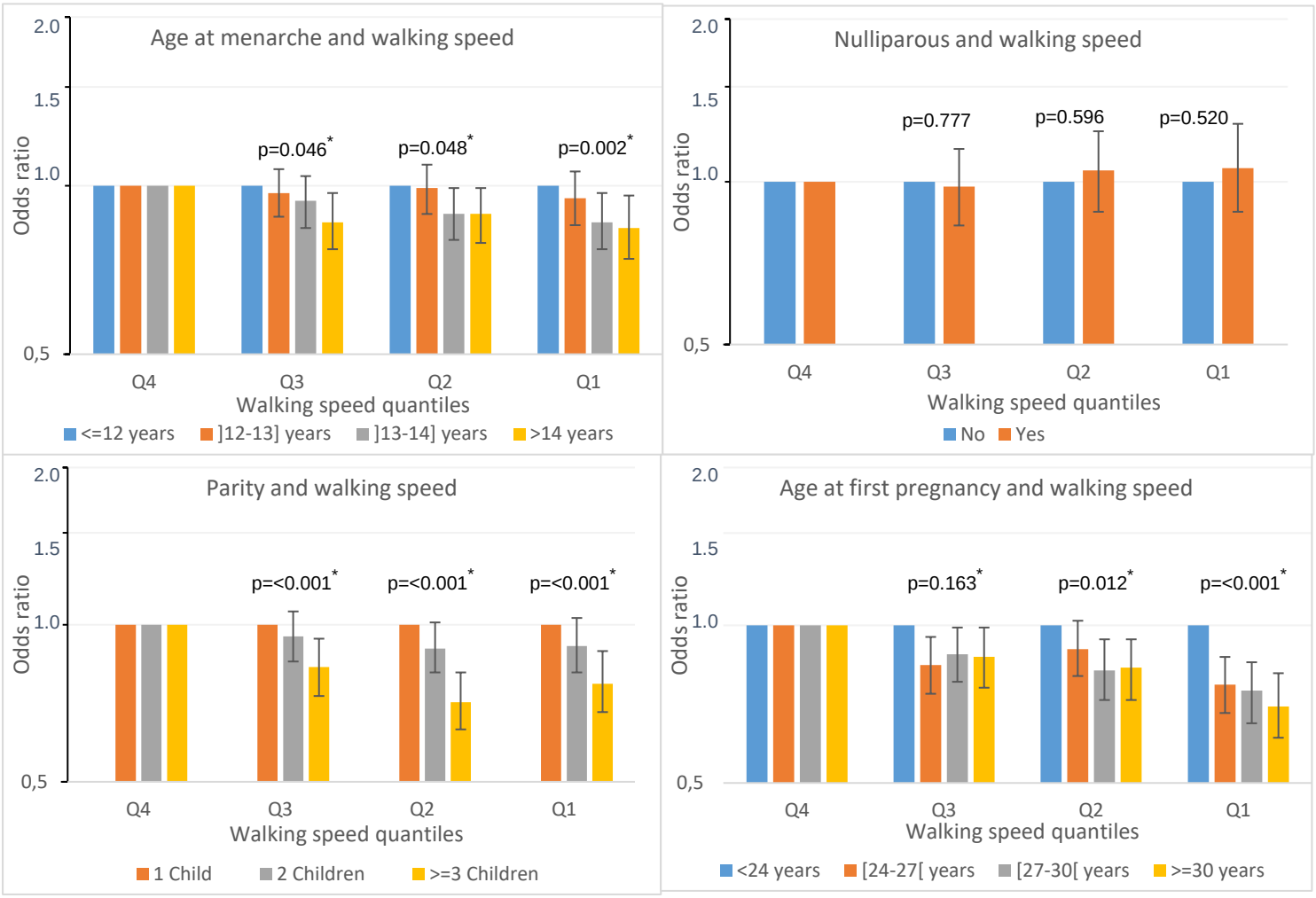
Figure 4: Association of walking speed with combined age and type of menopause

b. Multinomial logistic regression

In the second part of the analysis, WS was considered in quartiles and the multiadjusted model (model 3) is presented in Figures 4 and 5 below for all women and for menopausal women, respectively.

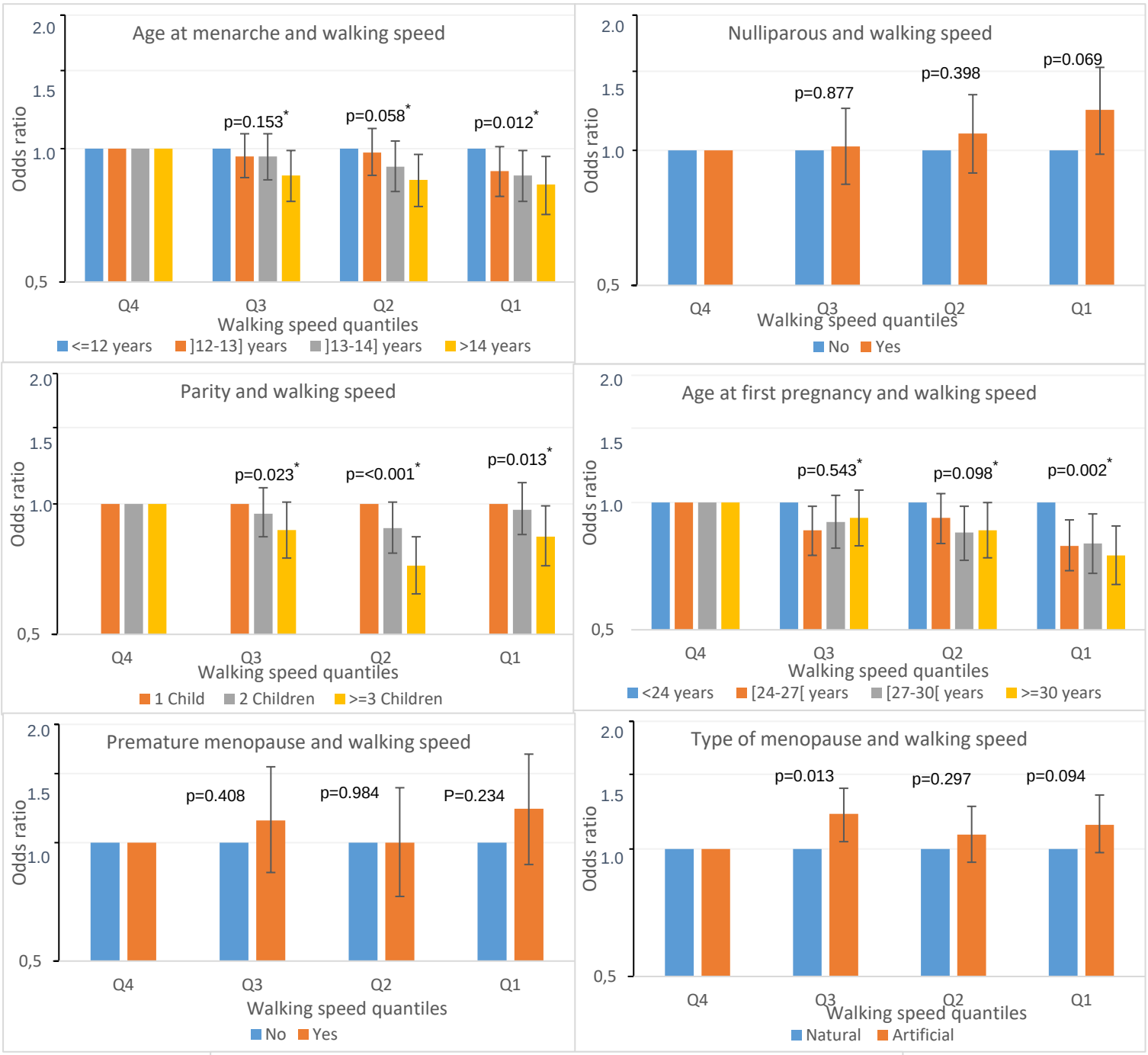
Overall, results were fully consistent with those observed in linear mixed models. Among all women, increased age at menarche, parity and age at first birth were associated with a lower risk to belong to the lower quartile of WS. Nevertheless as seen in Figures 5 and 6 the beneficial effect of older age at first pregnancy was not apparent in all women belonging to the 3rd quartile of WS whereas this effect was not significant for menopaused women in the 2nd and 3rd quartiles of WS. Similarly, the effect of older age at menarche in menopaused women was apparent only for women in the 1st WS quartile. The full multiadjusted models are seen in Appendices 12 & 13.

Among postmenopausal women, results of multinomial logistic regression also confirmed a beneficial impact of older age at menarche, increasing parity and older age at first birth. In addition, as shown in linear regression, we found no independent association of age and type of menopause and time since menopause with WS.



* p for linear trend

Figure 5: Multinomial logistic regression of walking speed with characteristics of reproductive life among all women (Model 3)



* p for linear trend

Figure 6: Multinomial logistic regression of walking speed with characteristics of reproductive life among postmenopausal women (model 3)

DISCUSSION

Using the data of the CONSTANCES Study, we found that, age at menarche, parity and age at first pregnancy could be independently associated with WS in all women, including menopaused women. We showed that an increase in age at menarche, age at first pregnancy and giving birth to an additional child were associated to an increase in WS. However, in our study, we found no independent association of WS with age at menopause, type of menopause, time since menopause and duration of reproductive life span. In addition, exogenous hormones, either contraceptives or HT, were not associated with WS.

Our results regarding the association of WS with parity and age at first birth were consistent with a previous study which found that nulliparity was associated with worst physical functioning (37). However, our findings were also inconsistent with those of other studies. A study investigating the association of physical performance with parity and maternal age at first birth did not find any association between these exposures and WS (7). This could be explained by the fact that nulliparous women were excluded from their study and their exposure variables were treated in 2 categories contrary to ours leading to a less precise analysis. Nevertheless, in CONSTANCES study, when using 2 categories of age at first birth with 18 years as a cut-off, we found that women who gave birth after 18 years walked faster (beta= -5.17, p=0.001 for women less than 18 years compared to those above 18 years). Another study reported that parity was not independently associated to physical performance after adjusting for age at first pregnancy and the association between early age at first birth and poor physical performance was no longer significant after they adjusted on chronic disease (38). However, participants in their study were older and increased parity seemed to be a consequence of early maternal age at first birth as in ours. Finally, a study in an ageing population in Turkey found that parity of 4 children or more was associated to disability (39). However, some difference between this study and ours can explain this discrepancy. First, contrary to the CONSTANCES study, physical performance was not objectively assessed but was self-reported in a questionnaire. In addition, women who were included were aged ≥65 and above.

To our knowledge, no previous study has investigated the association of age at menarche with physical performance later in life.

In our study, we found no significant association of menopausal status with WS but the influence of menopausal status on WS was explained by age (beta=-9.96, p<0.001 before adjustment for age). This results was consistent with previous data (40-42). Before mutual adjustment for exposure variables, we found that premature and artificial menopause were both associated with a slower WS but neither one nor the other was still significant in the

multiadjusted model. These results were consistent with data from the NHANES study where women with surgical and earlier age at menopause had worse physical functioning in older adulthood (40). Our result is also consistent with results from Sowers et al (30), who found that women with surgical menopause had an higher risk than women with natural menopause to present some or substantial limitations. In addition, we found that, before mutual adjustment, time since menopause was associated with slower WS whereas, duration of reproductive life span was not associate with WS. No previous study to the best of our knowledge has investigated the association of these reproductive life exposures with physical performance later in life. Finally, studies which investigated effects of HT on physical performance did not find an increased or decreased risk (43, 44) which was in line with our results. Although HT has been shown to offer protection against bone loss and maintain bone strength, its ability to improve physical performance has not been proved (45, 46).

Our results show that WS is associated to later age at menarche but not duration of reproductive life span. This does not support the hypothesis that lifetime cumulative exposure to oestrogens is protective but rather support the hypothesis that late lifetime cumulative exposure is protective. The positive association between late menarche and WS could be explained by the fact that early menarche has been associated to increased body fatness in adult women and greater risk of cardiovascular events (47-50) coupled with growing evidence of associations between physical performance and cardiovascular disease in elderly women (51, 52). Nevertheless, in our study, the association persisted despite adjustment for cardiovascular affections and hypercholesterolemia amongst others suggesting that other factors might play a role in this association.

Having 3 children or more was also associated to faster WS in our study which is contrary to the hypothesis that repeated pregnancies lead to a depletion of maternal physical resources (26). Women with more children have been shown to be at higher risk of cardiovascular disease and higher BMI which have both been identified as factors associated to functional decline in the elderly (48, 51-53). However, in our study, neither BMI nor cardiovascular affections could explain this association, but we could not rule out that residual confusion could lead to these results. Notwithstanding, this association could not be explained by biological factors such as hormonal exposure during pregnancy and childbearing, since a study showed that increased risk of cardiovascular disease with increase in number of children was similar in both men and women (48). Consequently, the association between repeated childbirth and faster WS could rather be explained by social, and behavioural factors related to parenthood and childbearing. Late age at first pregnancy was associated to faster WS in the women of our study. Studies have shown that early age at first birth was associated with unfavourable cardiovascular risk profiles and this was seen in both men and women

suggesting a social rather than biological pathway (38, 48, 54). Having a child at an early age could arise from or give rise to social consequences that increase the risk of developing chronic diseases and mobility loss in older age.

Sex hormones have the theoretical ability to modify physical performance but the inconsistent findings at the clinical level may be a result of individual variability in the level of sex hormones (55). Prior to our mutual adjustment in the third model, premature menopause and artificial menopause were associated to a decrease in WS in our second model, which is similar to the findings of literature (12). Early age at natural menopause has also been associated with higher risk of cardiovascular disease in elderly women (48) which is associated to functional decline in the elderly. Menopausal transition is associated with decline in sexual hormone, especially estradiol and progesterone (3, 12). However, this decline is abrupt and strong in artificial menopause with little residual circulating hormones. Muscular strength, cardiovascular/respiratory fitness, and cognitive function are all important determinants of physical performance and have been shown to be influenced by estrogens (30, 56-58). Hence, an abrupt and premature drop in these hormone levels could lead to a decrease in walking speed.

With puberty marking the onset of endogeneous oestrogen exposure in women and pregnancy being the source of an important surge in oestrogen levels in adult life; our results are in favour of later oestrogen exposure in adolescence and important oestrogen exposure later in adulthood being beneficial for physical performance.

Unlike like most of the previous studies, we examined the independent association of reproductive life characteristics on WS, through a multiadjusted model which included all the reproductive life characteristics which had an apparent association to WS. This enabled us to isolate the individual effect of each characteristic and represents an original contribution of our study.

The strengths of this study included the large sample size. CONSTANCES is a large cohort, including persons living and working in diverse settings, from large cities to small villages in different regions of France, with a broad range of socioeconomic status and trades. Added to this diversity, is the availability of detailed information on a large set of variables including reproductive factors and other lifestyle factors which enables us to account for a wide variety of confounding factors. This cohort also includes physical tests starting at 45 years, which is earlier in the life course than most cohorts and also enables us to study menopausal transition in this group. Lastly, the large sample size enabled us to study the effect of combined variables and to do sub-group analysis with adequate statistical power.

This study however has some limitations. Firstly, due to the voluntary participation of cohort members and an acceptance rate of <10%, CONSTANCES is not representative of the

French population and will probably be an underrepresentation of hard-to-reach subjects, therefore not generalizable to the overall French population. In addition, subjects with missing data of WS were rather different that those with motor tests. However, in our sample, all the known baseline characteristics associated with our outcome of interest (WS) and with the hormonal exposures were found, which is quite reassuring. Secondly, information on reproductive factors were self-reported and collected several years after the reproductive events occurred. This could lead recall bias which is likely to be non-differential and would underestimate the associations but would not explain the significant associations we found. Although our findings were robust to adjustment for several important confounders, we cannot exclude that the observed associations could have been due, at least partially, to residual confounding.

This analysis can be followed up in different ways. Firstly, prospects could include a stratified analysis on different age groups to see if that changed the observed associations. In addition, specific attention could be given to the time since onset of menopause exposure which was not significantly associated when considered as a continuous variable but was borderline in the multiadjusted polytomous model. Moreover, we could use imputed data of WS to take into account the issue of missing values of the subjects with WS data as compared to the overall subjects. Finally, we also plan to carry out similar analysis on other physical performance measures, including hand grip and balance.

CONCLUSION

In conclusion, our findings suggest that being exposure as late as possible in teenage years and to higher oestrogen concentrations later in adult life could be independent protective factors of functional decline in middle aged and elderly women, irrespective of cardiovascular risks factor and diseases, and cognitive function. Further studies are needed to identify the biological, behavioural and social mechanisms involved. Nevertheless, these findings could help health professionals to identify women who may be at risk since they present early puberty and/or early age at first pregnancy.

REFERENCES

1. WHO. Global health and ageing 2011 [February 28, 2019]. Available from: https://www.who.int/ageing/publications/global_health/en/.
2. United Nations Department of Economic and Social Affairs PD. World Population Ageing. United Nations; 2015.
3. Cauley JA, Petrini AM, Laporte RE, Sandler RB, Bayles CM, Robertson RJ, et al. THE DECLINE OF GRIP STRENGTH IN THE MENOPAUSE - RELATIONSHIP TO PHYSICAL-ACTIVITY, ESTROGEN USE AND ANTHROPOMETRIC FACTORS. Journal of Chronic Diseases. 1987;40(2):115-20.
4. American College of Sports M, Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minson CT, Nigg CR, et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. Med Sci Sports Exerc. 2009;41(7):1510-30.
5. Onder G, Penninx B, Lapuerta P, Fried LP, Ostir GV, Guralnik JM, et al. Change in physical performance over time in older women: The Women's Health and Aging Study. J Gerontol Ser A-Biol Sci Med Sci. 2002;57(5):M289-M93.
6. Leveille SG, Penninx B, Melzer D, Izmirlian G, Guralnik JM. Sex differences in the prevalence of mobility disability in old age: The dynamics of incidence, recovery, and mortality. J Gerontol Ser B-Psychol Sci Soc Sci. 2000;55(1):S41-S50.
7. Camara SM, Pirkle C, Moreira MA, Vieira MC, Vafaei A, Maciel AC. Early maternal age and multiparity are associated to poor physical performance in middle-aged women from Northeast Brazil: a cross-sectional community based study. BMC Womens Health. 2015;15:56.
8. Ferrucci L, Cooper R, Shardell M, Simonsick EM, Schrack JA, Kuh D. Age-Related Change in Mobility: Perspectives From Life Course Epidemiology and Geroscience. J Gerontol A Biol Sci Med Sci. 2016;71(9):1184-94.
9. Guralnik JM, Winograd CH. PHYSICAL PERFORMANCE-MEASURES IN THE ASSESSMENT OF OLDER PERSONS. Aging-Clin Exp Res. 1994;6(5):303-5.
10. Birnie K, Cooper R, Martin RM, Kuh D, Sayer AA, Alvarado BE, et al. Childhood socioeconomic position and objectively measured physical capability levels in adulthood: a systematic review and meta-analysis. PLoS One. 2011;6(1):e15564.
11. Cooper R, Kuh D, Cooper C, Gale CR, Lawlor DA, Matthews F, et al. Objective measures of physical capability and subsequent health: a systematic review. Age Ageing. 2011;40(1):14-23.
12. Cooper R, Mishra G, Clennell S, Guralnik J, Kuh D. Menopausal status and physical performance in midlife: findings from a British birth cohort study. Menopause. 2008;15(6):1079-85.
13. Nybo H, Petersen HC, Gaist D, Jeune B, Andersen K, McGue M, et al. Predictors of Mortality in 2,249 Nonagenarians—The Danish 1905-Cohort Survey. Journal of the American Geriatrics Society. 2003;51(10):1365-73.
14. Artaud F, Singh-Manoux A, Dugravot A, Tzourio C, Elbaz A. Decline in Fast Gait Speed as a Predictor of Disability in Older Adults. J Am Geriatr Soc. 2015;63(6):1129-36.
15. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, et al. Gait speed and survival in older adults. JAMA. 2011;305(1):50-8.
16. Cesari M. Role of Gait Speed in the Assessment of Older Patients. JAMA. 2011;305(1):93-4.
17. Rolland YM, Cesari M, Miller ME, Penninx BW, Atkinson HH, Pahor M. Reliability of the 400-M Usual-Pace Walk Test as an Assessment of Mobility Limitation in Older Adults. Journal of the American Geriatrics Society. 2004;52(6):972-6.
18. Reher D, Requena M. Living Alone in Later Life: A Global Perspective. Population and Development Review. 2018;44(3):427-54.
19. Samson MM, Meeuwsen I, Crowe A, Dessens JAG, Duursma SA, Verhaar HJJ. Relationships between physical performance measures, age, height and body weight in healthy adults. Age and Ageing. 2000;29(3):235-42.

20. Phillips SK, Rook KM, Siddle NC, Bruce SA, Woledge RC. MUSCLE WEAKNESS IN WOMEN OCCURS AT AN EARLIER AGE THAN IN MEN, BUT STRENGTH IS PRESERVED BY HORMONE REPLACEMENT THERAPY. Clin Sci. 1993;84(1):95-8.
21. El Khoudary SR, McClure CK, VoPham T, Karvonen-Gutierrez CA, Sternfeld B, Cauley JA, et al. Longitudinal assessment of the menopausal transition, endogenous sex hormones, and perception of physical functioning: the Study of Women's Health Across the Nation. J Gerontol A Biol Sci Med Sci. 2014;69(8):1011-7.
22. Horstman AM, Dillon EL, Urban RJ, Sheffield-Moore M. The role of androgens and estrogens on healthy aging and longevity. J Gerontol A Biol Sci Med Sci. 2012;67(11):1140-52.
23. Kurina LM, Gulati M, Everson-Rose SA, Chung PJ, Karavolos K, Cohen NJ, et al. The effect of menopause on grip and pinch strength: results from the Chicago, Illinois, site of the Study of Women's Health Across the Nation. Am J Epidemiol. 2004;160(5):484-91.
24. Sipila S, Finni T, Kovanen V. Estrogen influences on neuromuscular function in postmenopausal women. Calcif Tissue Int. 2015;96(3):222-33.
25. Hank K. Childbearing history, later-life health, and mortality in Germany. Popul Stud-J Demogr. 2010;64(3):275-91.
26. Hurt LS, Ronsmans C, Thomas SL. The effect of number of births on women's mortality: systematic review of the evidence for women who have completed their childbearing. Popul Stud (Camb). 2006;60(1):55-71.
27. Umberson D, Liu H, Mirowsky J, Reczek C. Parenthood and trajectories of change in body weight over the life course. Soc Sci Med. 2011;73(9):1323-31.
28. Hardy R, Lawlor DA, Black S, Mishra GD, Kuh D. Age at birth of first child and coronary heart disease risk factors at age 53 years in men and women: British birth cohort study. J Epidemiol Community Health. 2009;63(2):99-105.
29. Bassey EJ, Mockett SP, Fentem PH. Lack of variation in muscle strength with menstrual status in healthy women aged 45-54 years: Data from a national survey. Eur J Appl Physiol Occup Physiol. 1996;73(3-4):382-6.
30. Sowers M, Tomey K, Jannausch M, Eyvazzadeh A, Nan B, Randolph J, Jr. Physical functioning and menopause states. Obstet Gynecol. 2007;110(6):1290-6.
31. Zins M, Bonenfant S, Carton M, Coeuret-Pellicer M, Guéguen A, Gourmelen J, et al. The CONSTANCES cohort: an open epidemiological laboratory. BMC Public Health. 2010;10(1):479.
32. CONSTANCES. Actualités 2019 [March 04, 2019]. Available from: http://www.constances.fr/.
33. Zins M, Goldberg M. The Constances Cohort 2015 [February 28, 2019]. Available from: http://www.constances.fr/assets/pdf/Scientific-protocol-01-2015.pdf.
34. Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. Age Ageing. 1997;26(1):15-9.
35. Ko S-u, Stenholm S, Metter EJ, Ferrucci L. Age-associated gait patterns and the role of lower extremity strength - results from the Baltimore Longitudinal Study of Aging. Archives of gerontology and geriatrics. 2012;55(2):474-9.
36. VanderWeele TJ. Principles of confounder selection. Eur J Epidemiol. 2019;34(3):211-9.
37. Harville EW, Chen W, Guralnik J, Bazzano LA. Reproductive history and physical functioning in midlife: The Bogalusa Heart Study. Maturitas. 2018;109:26-31.
38. Pirkle CM, de Albuquerque Sousa ACP, Alvarado B, Zunzunegui M-V, Group IR. Early maternal age at first birth is associated with chronic diseases and poor physical performance in older age: cross-sectional analysis from the International Mobility in Aging Study. BMC public health. 2014;14:293-.
39. Akin B, Ege E, Kocoglu D, Arslan SY, Bilgili N. Reproductive history, socioeconomic status and disability in the women aged 65 years or older in Turkey. Arch Gerontol Geriatr. 2010;50(1):11-5.
40. Tom SE, Cooper R, Patel KV, Guralnik JM. Menopausal characteristics and physical functioning in older adulthood in the National Health and Nutrition Examination Survey III. Menopause. 2012;19(3):283-9.
41. Bondarev D, Laakkonen EK, Finni T, Kokko K, Kujala UM, Aukee P, et al. Physical performance in relation to menopause status and physical activity. Menopause. 2018;25(12):1432-41.

42. da Camara SM, Zunzunegui MV, Pirkle C, Moreira MA, Maciel AC. Menopausal status and physical performance in middle aged women: a cross-sectional community-based study in Northeast Brazil. PLoS One. 2015;10(3):e0119480.
43. Greenspan SL, Resnick NM, Parker RA. The effect of hormone replacement on physical performance in community-dwelling elderly women. Am J Med. 2005;118(11):1232-9.
44. Michael YL, Gold R, Manson JE, Keast EM, Cochrane BB, Woods NF, et al. Hormone therapy and physical function change among older women in the Women's Health Initiative: a randomized controlled trial. Menopause. 2010;17(2):295-302.
45. Uusi-Rasi K, Beck TJ, Sievänen H, Heinonen A, Vuori I. Associations of hormone replacement therapy with bone structure and physical performance among postmenopausal women☆. Bone. 2003;32(6):704-10.
46. Uusi-Rasi K, Sievanen H, Heinonen A, Beck TJ, Vuori I. Determinants of changes in bone mass and femoral neck structure, and physical performance after menopause: a 9-year follow-up of initially peri-menopausal women. Osteoporos Int. 2005;16(6):616-22.
47. Feng Y, Hong X, Wilker E, Li Z, Zhang W, Jin D, et al. Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases. Atherosclerosis. 2008;196(2):590-7.
48. Peters SAE, Woodward M. Women's reproductive factors and incident cardiovascular disease in the UK Biobank. Heart. 2018;104(13):1069.
49. Merritt MA, Riboli E, Murphy N, Kadi M, Tjønneland A, Olsen A, et al. Reproductive factors and risk of mortality in the European Prospective Investigation into Cancer and Nutrition; a cohort study. BMC Medicine. 2015;13(1):252.
50. Gallagher LG, Davis LB, Ray RM, Psaty BM, Gao DL, Checkoway H, et al. Reproductive history and mortality from cardiovascular disease among women textile workers in Shanghai, China. International Journal of Epidemiology. 2011;40(6):1510-8.
51. Stefanick ML, Brunner RL, Leng X, Limacher MC, Bird CE, Garcia DO, et al. The Relationship of Cardiovascular Disease to Physical Functioning in Women Surviving to Age 80 and Above in the Women's Health Initiative. J Gerontol A Biol Sci Med Sci. 2016;71 Suppl 1:S42-53.
52. Pettee KK, Larouere BM, Kriska AM, Delia Johnson B, Orchard TJ, Goodpaster BH, et al. Associations Among Walking Performance, Physical Activity, and Subclinical Cardiovascular Disease. Preventive Cardiology. 2007;10(3):134-40.
53. Abrams B, Heggeseth B, Rehkopf D, Davis E. Parity and body mass index in US women: a prospective 25-year study. Obesity (Silver Spring). 2013;21(8):1514-8.
54. Hardy R, Lawlor DA, Black S, Mishra GD, Kuh D. Age at birth of first child and coronary heart disease risk factors at age 53 years in men and women: British birth cohort study. Journal of epidemiology and community health. 2009;63(2):99-105.
55. Tenan M, Hackney AC. Sex hormones and the nervous system, do they matter for physical performance? Journal of Science and Medicine in Sport. 2017;20:S14.
56. Kuh D, Bassey EJ, Butterworth S, Hardy R, Wadsworth ME, Musculoskeletal Study T. Grip strength, postural control, and functional leg power in a representative cohort of British men and women: associations with physical activity, health status, and socioeconomic conditions. J Gerontol A Biol Sci Med Sci. 2005;60(2):224-31.
57. Hayashida I, Tanimoto Y, Takahashi Y, Kusabiraki T, Tamaki J. Correlation between muscle strength and muscle mass, and their association with walking speed, in community-dwelling elderly Japanese individuals. PLoS One. 2014;9(11):e111810.
58. Shuster LT, Rhodes DJ, Gostout BS, Grossardt BR, Rocca WA. Premature menopause or early menopause: long-term health consequences. Maturitas. 2010;65(2):161-6.

APPENDICES

Appendix 1: Ethics approval

Department of Economics/ScHARR

Research Ethics Review
for Undergraduate and Postgraduate-Taught Students

Form 1C: Student Declaration

To be included in Appendices of dissertation

→ **Research Project Title: Hormonal exposure and physical performances in women in general population. The CONSTANCES study**

→ **Name of dataset to be used: CONSTANCES**

Owner of dataset:

Total number of datasets to be used: ...1.. **If more than one, then fill in a separate declaration for each dataset.**

State the case that applies to your research project: Case ..2..

Case 1: Your proposed project will only involve anonymised/aggregated data that any member of the public is legitimately free to access and use without having to obtain permission from anyone else. E.g., macroeconomic statistics provided by legitimate sources such as government departments and international organisations; anonymised secondary data on individuals or firms provided by legitimate sources such as government departments and which do not require any form of registration or statement of purpose to allow access.

Case 2: Your proposed project will involve anonymised secondary data for which you need to obtain permission from the owner (e.g., you need to satisfy some condition before being permitted to download the data, such as a declaration of intended educational purpose. Downloading the BHPS from the Data Archive falls in this category.)

Case 3: None of the above cases. Note that the department does not allow undergraduate or postgraduate taught students to use primary data, or secondary data that may include personal data, unless specific training is undertaken by the student.

→ If your proposed project falls within Case 1, then simply print your name, date and sign below.
If your proposed project falls within Case 2, then you need to append to this form evidence that you have legitimately obtained access to these data. E.g.,

confirmation email, and statement of purpose if one was required. Then print your name, date and sign below.
If your proposed project falls within Case 3, then contact your supervisor or supervisory team as soon as possible. You may not be able to use the proposed data.

→ **Name of student:** Aude NDOADOUMGUE

→ **Signature of student:** [signature] **Date:** FEBRUARY 27 st, 2019

→ **Name of supervisor:** Marianne CANOMO

→ **Signature of Supervisor:** [signature] **Date:** Feb 21, 2019.

Appendix 2: Baseline characteristics and their association with age at menarche

Characteristics	Age at menarche				p for trend	p* for trend
	<12	[12-13[	[13-14[	>= 14		
N (%)	9484 (40.6)	5518 (23.6)	4511 (19.3)	3824 (16.4)		
Age yr						
[45-50[	1669 (17.6)	1108 (20.1)	849 (18.8)	758 (19.8)		
[50-55[	1833 (19.2)	1061 (19.2)	935 (20.7)	815 (21.2)		
[55-60[	2035 (21.5)	1165 (21.1)	877 (19.4)	826 (21.6)	<0.001	
[60-65[	1958 (20.7)	1070 (19.4)	877 (19.4)	735 (19.2)		
>= 65	1989 (21.0)	1114 (20.2)	973 (21.7)	690 (18.0)		
Height cm (MV=732)						
<157	2160 (23.5)	955 (17.8)	769 (17.6)	560 (15.2)		
[157-161[	2871 (31.2)	1541 (28.8)	1193 (27.3)	1002 (27.2)	<0.001	<0.001
[161-166[	2199 (23.9)	1362 (25.4)	1060 (24.3)	938 (25.5)		
>=166	1973 (21.4)	1502 (28.0)	1341 (30.8)	1179 (32.1)		
BMI kg/m² (MV=975)						
< 25	4813 (52.9)	3278 (61.9)	2800 (64.8)	2448 (67.1)		
25 - 30	2746 (30.2)	1397 (26.4)	1086 (25.1)	851 (23.4)	<0.001	<0.001
>=30	1539 (16.9)	623 (11.7)	436 (10.1)	345 (9.5)		
Marital status (MV=532)						
In a relationship	5959 (64.1)	3507 (65.1)	2828 (64.2)	2262 (60.9)		
Single	1238 (13.4)	749 (13.9)	588 (13.3)	574 (15.5)	0.008	0.016
Separated/Divorced/Widow	2094 (22.5)	1135 (21.0)	991 (22.5)	880 (23.6)		
Revenues (MV=2116)						
<45€ - <1500€	842 (9.8)	427 (8.5)	403 (9.8)	415 (12.0)		
1500€ - <2180€	2567 (29.8)	1326 (26.5)	1170 (28.4)	1055 (30.5)	0.003	0.001
2180€ - 4200€ +	5219 (60.4)	3260 (65.0)	2549 (61.8)	1988 (57.5)		
Education (MV=427)						
No education/Primary education	2765 (29.7)	1435 (26.5)	1333 (30.1)	1270 (33.9)		
High school degree	1779 (19.1)	929 (17.1)	787 (17.8)	604 (16.1)	0.019	0.002
Bachelor's degree	3378 (36.2)	2063 (38.1)	1607 (36.2)	1315 (35.2)		
Master's Degree/PhD/Others	1396 (15.0)	993 (18.3)	703 (15.9)	553 (14.8)		
Physical activity (MV=1150)						
Inactive	2003 (22.2)	1073 (20.3)	859 (20.2)	818 (22.6)		
Moderately active	3923 (43.4)	2401 (45.5)	1950 (45.7)	1548 (42.8)	0.725	0.187
Very active	3105 (34.4)	1801 (34.2)	1454 (34.1)	1252 (34.6)		
Alcohol consumption (MV=3207)						
No consumption	1580 (19.3)	834 (17.2)	632 (16.3)	589 (18.2)		
Moderate consumption	5946 (72.7)	3576 (73.9)	2870 (74.2)	2350 (72.6)	0.001	<0.001
Unsafe consumption	656 (8.0)	432 (8.9)	366 (9.5)	299 (9.2)		
Smoking status (MV=1070)						
Never	4731 (52.1)	2654 (50.2)	2185 (50.8)	1789 (49.5)		
Past	1134 (12.5)	685 (13.0)	606 (14.1)	586 (16.2)	<0.001	<0.001
Current	3208 (35.4)	1945 (36.8)	1507 (35.1)	1237 (34.3)		
Diabetes						
No	9249 (97.5)	5433 (98.5)	4433 (98.3)	3752 (98.1)	0.005	0.012
Yes	235 (2.5)	85 (1.5)	78 (1.7)	72 (1.9)		
Hypertension (MV=14)						
No	6251 (65.9)	3797 (68.9)	3094 (68.6)	2677 (70.0)	<0.001	<0.001
Yes	3229 (34.1)	1714 (31.1)	1415 (31.4)	1146 (30.0)		
Hypercholesterolemia (MV=12)						
No	6062 (64.0)	3646 (66.1)	2933 (65.0)	2568 (67.2)	0.001	0.036
Yes	3417 (36.1)	1867 (33.9)	1577 (35.0)	1255 (32.8)		
Depression (MV=304)						
No	7018 (75.0)	4198 (77.0)	3374 (75.9)	2916 (77.1)	0.016	0.020
Yes	2338 (25.0)	1255 (23.0)	1072 (24.1)	864 (22.9)		
MMSE (MV=136)						
>=29	5023 (53.3)	3094 (56.3)	2448 (54.5)	1900 (50.1)		
28	1829 (19.4)	1028 (18.7)	874 (19.5)	726 (19.2)	0.006	0.003
<28	2576 (27.3)	1371 (25.0)	1169 (26.0)	1163 (30.7)		
Respiratory affections (MV=313)						
No	8506 (91.0)	4937 (90.6)	4070 (91.3)	3422 (90.8)	0.892	0.829
Yes	845 (9.0)	512 (9.4)	386 (8.7)	346 (9.2)		
Renal affections (MV=348)						
No	9288 (99.5)	5430 (99.7)	4427 (99.8)	3759 (99.6)	0.445	0.490
Yes	42 (0.5)	16 (0.3)	10 (0.2)	17 (0.4)		

Appendix 2: follows

Characteristics	Age at menarche				p for trend	p* for trend
	<12	[12-13[	[13-14[	>= 14		
Cardiovascular affections (MV=324)						
No	9159 (98.0)	5357 (98.4)	4382 (98.4)	3703 (98.1)	0.407	0.556
Yes	182 (2.0)	89 (1.6)	71 (1.6)	70 (1.9)		
Arthritis (MV=594)						
No	9076 (98.1)	5287 (98.5)	4304 (98.2)	3671 (98.2)	0.491	0.538
Yes	180 (1.9)	81 (1.5)	77 (1.8)	67 (1.8)		
Cancer of ovaries and uterus						
No	9364 (98.7)	5453 (98.8)	4448 (98.6)	3776 (98.7)	0.790	0.726
Yes	120 (1.3)	65 (1.2)	63 (1.4)	48 (1.3)		

MV : missing values
BMI : body mass index
*** : adjusted for age**

Appendix 3: Baseline characteristics and their association with parity

Characteristics	Parity				p for trend	p* for trend
	0	1	2	>=3		
N (%)	2184 (9.5)	4139 (17.9)	10296 (44.6)	6462 (28.0)		
Age yr						
[45-50[	490 (22.4)	745 (18.0)	1958 (19.0)	1131 (17.5)		
[50-55[	470 (21.5)	769 (18.6)	2050 (19.9)	1381 (21.4)		
[55-60[	427 (19.6)	828 (20.0)	2151 (20.9)	1418 (21.9)	0.265	
[60-65[	401 (18.4)	877 (21.2)	2019 (19.6)	1314 (20.3)		
>= 65	396 (18.1)	920 (22.2)	2118 (20.6)	1218 (18.9)		
Height cm (MV=731)						
<157	417 (19.8)	845 (21.0)	1970 (19.7)	1157 (18.6)		
[157-161[	617 (29.3)	1180 (29.4)	2978 (29.8)	1756 (28.2)	0.001	0.001
[161-166[	486 (23.1)	999 (24.9)	2472 (24.8)	1545 (24.7)		
>=166	588 (27.8)	993 (24.7)	2570 (25.7)	1777 (28.5)		
BMI kg/m² (MV=978)						
< 25	1295 (62.1)	2375 (59.9)	5984 (60.5)	3483 (56.5)		
25 - 30	491 (23.5)	1067 (26.9)	2741 (27.7)	1735 (28.2)	<0.001	<0.001
>=30	300 (14.4)	525 (13.2)	1162 (11.8)	945 (15.3)		
Marital status (MV=522)						
In a relationship	676 (31.6)	2221 (55.0)	7099 (70.6)	4661 (73.7)		
Single	1241 (57.9)	705 (17.5)	598 (6.0)	206 (3.3)	<0.001	<0.001
Separated/Divorced/Widow	225 (10.5)	1115 (27.5)	2357 (23.4)	1455 (23.0)		
Revenues (MV=2119)						
<45€ - <1500€	294 (14.7)	457 (12.2)	712 (7.6)	561 (9.6)		
1500€ - <2180€	777 (38.8)	1264 (33.8)	2460 (26.2)	1468 (25.2)	<0.001	<0.001
2180€ - 4200€ +	930 (46.5)	2017 (54.0)	6231 (66.4)	3791 (65.2)		
Education (MV=421)						
No education/Primary education	442 (20.6)	1385 (34.0)	3144 (31.1)	1900 (29.9)		
High school degree	356 (16.6)	780 (19.2)	1913 (18.9)	1006 (15.9)	0.013	0.028
Bachelor's degree	884 (41.3)	1373 (33.8)	3635 (36.0)	2319 (36.5)		
Master's Degree/PhD/Others	460 (21.5)	530 (13.0)	1411 (14.0)	1122 (17.7)		
Physical activity (MV=1160)						
Inactive	497 (23.7)	843 (21.6)	2055 (21.0)	1287 (21.1)		
Moderately active	966 (46.0)	1748 (44.7)	4285 (43.7)	2722 (44.5)	0.001	0.001
Very active	636 (30.3)	1318 (33.7)	3462 (35.3)	2102 (34.4)		
Alcohol consumption (MV=3209)						
No consumption	388 (20.3)	666 (18.9)	1567 (17.4)	997 (18.4)		
Moderate consumption	1324 (69.2)	2540 (72.1)	6735 (74.7)	3968 (73.1)	0.945	0.988
Unsafe consumption	200 (10.5)	315 (9.0)	711 (7.9)	461 (8.5)		
Smoking status (MV=1055)						
Never	1108 (52.7)	1854 (47.0)	5082 (51.7)	3347 (54.5)		
Past	273 (13.0)	635 (16.1)	1249 (12.7)	741 (12.1)	<0.001	<0.001
Current	722 (34.3)	1457 (36.9)	3505 (35.6)	2053 (33.4)		

Appendix 3: follows

Characteristics	Parity				p for trend	p* for trend
	0	1	2	>=3		
Diabetes						
No	2139 (97.9)	4063 (98.2)	10118 (98.3)	6289 (97.3)	0.013	0.013
Yes	45 (2.1)	76 (1.8)	178 (1.7)	173 (2.7)		
Hypertension (MV=15)						
No	1537 (70.4)	2778 (67.2)	7018 (68.2)	4292 (66.4)	0.006	0.009
Yes	645 (29.6)	1359 (32.8)	3269 (31.8)	2168 (33.6)		
Hypercholesterolemia (MV=14)						
No	1478 (67.7)	2690 (65.0)	6671 (64.9)	4177 (64.7)	0.038	0.096
Yes	706 (32.3)	1448 (35.0)	3614 (35.1)	2283 (35.3)		
Depression (MV=309)						
No	1629 (75.5)	3026 (74.2)	7779 (76.7)	4891 (76.5)	0.028	0.023
Yes	528 (24.5)	1053 (25.8)	2364 (23.3)	1502 (23.5)		
MMSE (MV=128)						
>=29	1235 (57.2)	2085 (50.7)	5478 (53.5)	3471 (54.0)		
28	390 (18.1)	823 (20.0)	1969 (19.2)	1190 (18.5)	0.610	0.661
<28	535 (24.7)	1205 (29.3)	2801 (27.3)	1771 (27.5)		
Respiratory affections (MV=315)						
No	1965 (91.1)	3679 (90.2)	9311 (91.8)	5765 (90.3)	0.626	0.583
Yes	191 (8.9)	401 (9.8)	832 (8.2)	622 (9.7)		
Renal affections (MV=357)						
No	2145 (99.7)	4054 (99.5)	10088 (99.7)	6355 (99.6)	0.980	0.964
Yes	7 (0.3)	19 (0.5)	30 (0.3)	26 (0.4)		
Cardiovascular affections (MV=330)						
No	2125 (98.5)	3998 (98.1)	9962 (98.3)	6265 (98.1)	0.461	0.480
Yes	33 (1.5)	78 (1.9)	168 (1.7)	122 (1.9)		
Arthritis (MV=598)						
No	2095 (98.5)	3952 (98.0)	9813 (98.1)	6218 (98.4)	0.927	0.894
Yes	31 (1.5)	79 (2.0)	191 (1.9)	104 (1.6)		
Cancer of ovaries and uterus						
No	2156 (98.7)	4071 (98.4)	10187 (98.9)	6376 (98.7)	0.429	0.426
Yes	28 (1.3)	68 (1.6)	109 (1.1)	86 (1.3)		

MV : missing values
BMI : body mass index
*** : adjusted for age**

Appendix 4: Baseline characteristics and their association with age at first pregnancy

Characteristics	Age at first pregnancy				p for trend	p* for trend
	<24	[24-27[	[27-30[	>= 30		
N (%)	5614 (27.0)	5367 (25.8)	4507 (21.7)	5311 (25.5)		
Age yr						
[45-50[	537 (9.5)	822 (15.2)	1069 (23.7)	1387 (26.2)		
[50-55[	847 (15.1)	1077 (20.1)	1011 (22.4)	1248 (23.5)		
[55-60[	1209 (21.5)	1136 (21.2)	938 (20.8)	1091 (20.5)	<0.001	
[60-65[	1435 (25.6)	1114 (20.8)	765 (17.0)	882 (16.6)		
>= 65	1586 (28.3)	1218 (22.7)	724 (16.1)	703 (13.2)		
Height cm (MV=652)						
<157	1428 (26.3)	1003 (19.2)	675 (15.5)	838 (16.3)		
[157-161[	1741 (32.0)	1507 (28.9)	1216 (28.0)	1422 (27.6)	<0.001	<0.001
[161-166[	1217 (22.4)	1293 (24.8)	1187 (27.3)	1302 (25.3)		
>=166	1051 (19.3)	1409 (27.1)	1273 (29.2)	1585 (30.8)		
BMI kg/m² (MV=877)						
< 25	2664 (49.5)	3090 (60.2)	2769 (64.3)	3283 (64.4)		
25 - 30	1745 (32.4)	1423 (27.7)	1069 (24.8)	1269 (24.9)	<0.001	<0.001
>=30	972 (18.1)	622 (12.1)	470 (10.9)	546 (10.7)		
Marital status (MV=469)						
In a relationship	3712 (68.0)	3801 (72.1)	3086 (69.9)	3334 (64.4)		
Single	188 (3.4)	199 (3.8)	276 (6.2)	834 (16.1)	<0.001	<0.001
Separated/Divorced/Widow	1562 (28.6)	1273 (24.1)	1053 (23.9)	1012 (19.5)		

Appendix 4: follows

Characteristics	Age at first pregnancy				p for trend	p* for trend
	<24	[24-27[	[27-30[	>= 30		
Revenues (MV=1920)						
<45€ - <1500€	738 (14.7)	343 (7.1)	258 (6.3)	364 (7.5)		
1500€ - <2180€	1827 (36.3)	1307 (26.9)	891 (21.7)	1144 (23.4)	<0.001	<0.001
2180€ - 4200€ +	2463 (49.0)	3211 (66.0)	2962 (72.0)	3371 (69.1)		
Education (MV=369)						
No education/Primary education	3104 (56.5)	1568 (29.7)	862 (19.4)	856 (16.4)		
High school degree	1087 (19.8)	1126 (21.3)	743 (16.8)	729 (14.0)	<0.001	<0.001
Bachelor's degree	1055 (19.2)	2005 (37.9)	1946 (43.9)	2296 (44.0)		
Master's Degree/PhD/Others	246 (4.5)	586 (11.1)	883 (19.9)	1338 (25.6)		
Physical activity (MV=1061)						
Inactive	1135 (21.9)	960 (18.8)	844 (19.5)	1217 (23.7)		
Moderately active	2160 (41.7)	2229 (43.7)	1969 (45.5)	2367 (46.2)	<0.001	0.777
Very active	1889 (36.4)	1913 (37.5)	1513 (35.0.)	1542 (30.1)		
Alcohol consumption (MV=2907)						
No consumption	929 (20.2)	790 (16.9)	690 (17.3)	806 (17.4)		
Moderate consumption	3296 (71.8)	3498 (74.8)	2979 (74.7)	3425 (73.9)	0.003	<0.001
Unsafe consumption	367 (8.0)	389 (8.3)	318 (8.0)	405 (8.7)		
Smoking status (MV=965)						
Never	2969 (55.9)	2674 (51.9)	2194 (51.0)	2388 (47.1)		
Past	639 (12.0)	688 (13.4)	556 (12.9)	731 (14.4)	<0.001	<0.001
Current	1704 (32.1)	1786 (34.7)	1551 (36.1)	1954 (38.5)		
Diabetes						
No	5410 (96.4)	5273 (98.2)	4445 (98.6)	5249 (98.8)	<0.001	<0.001
Yes	204 (3.6)	94 (1.8)	62 (1.4)	62 (1.2)		
Hypertension (MV=13)						
No	3238 (57.7)	3551 (66.2)	3267 (72.6)	3976 (74.9)	<0.001	<0.001
Yes	2371 (42.3)	1814 (33.8)	1235 (27.4)	1334 (25.1)		
Hypercholesterolemia (MV=14)						
No	3183 (56.8)	3336 (62.2)	3117 (69.2)	3839 (72.3)	<0.001	<0.001
Yes	2425 (43.2)	2030 (37.8)	1384 (30.8)	1471 (27.7)		
Depression (MV=282)						
No	4006 (72.2)	4045 (76.4)	3468 (78.2)	4102 (78.3)	<0.001	<0.001
Yes	1545 (27.8)	1247 (23.6)	967 (21.8)	1137 (21.7)		
MMSE (MV=102)						
>=29	2431 (43.5)	2886 (54.0)	2641 (58.8)	3042 (57.6)		
28	1145 (20.5)	1042 (19.5)	807 (18.0)	972 (18.4)	<0.001	<0.001
<28	2009 (36.0)	1413 (26.5)	1044 (23.2)	1265 (24.0)		
Respiratory affections (MV=287)						
No	5015 (90.4)	4800 (90.7)	4059 (91.6)	4796 (91.5)	0.017	0.001
Yes	533 (9.6)	491 (9.3)	374 (8.4)	444 (8.5)		
Renal affections (MV=324)						
No	5506 (99.6)	5256 (99.5)	4419 (99.8)	5223 (99.7)	0.085	0.212
Yes	22 (0.4)	25 (0.5)	10 (0.2)	14 (0.3)		
Cardiovascular affections (MV=304)						
No	5386 (97.3)	5199 (98.3)	4367 (98.6)	5179 (98.8)	<0.001	<0.001
Yes	152 (2.7)	91 (1.7)	60 (1.4)	61 (1.2)		
Arthritis (MV=540)						
No	5363 (97.7)	5127 (98.1)	4297 (98.3)	5100 (98.6)	<0.001	0.001
Yes	129 (2.3)	98 (1.9)	75 (1.7)	70 (1.4)		
Cancer of ovaries and uterus						
No	5519 (98.3)	5309 (98.9)	4459 (98.9)	5252 (98.9)	0.009	0.032
Yes	95 (1.7)	58 (1.1)	48 (1.1)	59 (1.1)		

MV : missing values
BMI : body mass index
*** : adjusted for age**

Appendix 5: Baseline characteristics and their association with type of menopause

Characteristics		Type of menopause		p value	p* value
		Natural	Artificial		
N (%)		15969 (86.3)	2542 (13.7)		
Age yr					
	[45-50[	570 (3.6)	217 (8.4)		
	[50-55[	2439 (15.2)	421 (16.6)		
	[55-60[	4372 (27.4)	549 (21.6)	<0.001	
	[60-65[	4308 (27.0)	609 (24.0)		
	>= 65	4280 (26.8)	746 (29.4)		
Height cm (MV=568)					
	<157	3429 (22.2)	564 (22.9)		
	[157-161[	4689 (30.2)	784 (31.8)	0.222	0.116
	[161-166[	3710 (24.0)	567 (23.0)		
	>=166	3650 (23.6)	550 (22.3)		
BMI kg/m² (MV=764)					
	< 25	9054 (59.1)	1215 (49.9)		
	25 - 30	4270 (27.9)	790 (32.4)	<0.001	<0.001
	>=30	1986 (13.0)	432 (17.7)		
Marital status (MV=429)					
	In a relationship	9915 (63.5)	1616 (65.2)		
	Single	1986 (12.8)	249 (10.1)	0.001	<0.001
	Separated/Divorced/Widow	3703 (23.7)	613 (24.7)		
Revenues (MV=1834)					
	<45€ - <1500€	1483 (10.3)	270 (12.0)		
	1500€ - <2180€	4372 (30.3)	742 (32.9)	0.001	0.003
	2180€ - 4200€ +	8563 (59.4)	1247 (55.1)		
Education (MV=367)					
	No education/Primary education	5093 (32.5)	1011 (40.6)		
	High school degree	2859 (18.3)	452 (18.2)	<0.001	<0.001
	Bachelor's degree	5434 (34.7)	761 (30.6)		
	Master's Degree/PhD/Others	2267 (14.5)	267 (10.6)		
Physical activity (MV=1079)					
	Inactive	2914 (19.4)	509 (21.3)		
	Moderately active	6522 (43.3)	987 (41.4)	0.052	0.100
	Very active	5611 (37.3)	889 (37.3)		
Alcohol consumption (MV=2709)					
	No consumption	2403 (17.6)	427 (19.8)		
	Moderate consumption	9989 (73.2)	1537 (71.3)	0.046	0.100
	Unsafe consumption	1255 (9.2)	191 (8.9)		
Smoking status (MV=888)					
	Never	7862 (51.8)	1333 (54.8)		
	Past	1890 (12.4)	248 (10.2)	0.002	<0.001
	Current	5438 (35.8)	852 (35.0)		
Diabetes					
	No	15609 (97.8)	2453 (96.5)	0.001	<0.001
	Yes	360 (2.2)	89 (3.5)		
Hypertension (MV=14)					
	No	10206 (64.0)	1440 (56.7)	<0.001	<0.001
	Yes	5752 (36.0)	1099 (43.3)		
Hypercholesterolemia (MV=14)					
	No	9458 (59.3)	1449 (57.1)	0.039	0.003
	Yes	6501 (40.7)	1089 (42.9)		
Depression (MV=246)					
	No	11925 (75.7)	1768 (70.6)	<0.001	<0.001
	Yes	3835 (24.3)	737 (29.4)		
MMSE (MV=107)					
	>=29	8234 (51.9)	1242 (49.1)		
	28	3072 (19.3)	510 (20.1)	0.025	0.042
	<28	4565 (28.8)	781 (30.8)		
Respiratory affections (MV=252)					
	No	14403 (91.4)	2241 (89.5)	0.002	0.002
	Yes	1352 (8.6)	263 (10.5)		
Renal affections (MV=294)					
	No	15658 (99.6)	2479 (99.5)	0.503	0.608
	Yes	67 (0.4)	13 (0.5)		

Appendix 5: follows

Characteristics	Type of menopause		p value	p* value
	Natural	Artificial		
Cardiovascular affections (MV=269)				
No	15432 (98.0)	2422 (97.0)	0.001	0.001
Yes	313 (2.0)	75 (3.0)		
Arthritis (MV=494)				
No	15263 (98.1)	2406 (97.7)	0.137	0.121
Yes	291 (1.9)	57 (2.3)		
Cancer of ovaries and uterus				
No	15847 (99.2)	2385 (93.8)	<0.001	<0.001
Yes	122 (0.8)	157 (6.2)		

MV : missing values
BMI : body mass index
*** : adjusted for age**

Appendix 6: Baseline characteristics and their association with age at menopause

Characteristics	Age at menopause				P for trend	p* for trend
	Premature	Early	Normal	Late		
N (%)	544 (3.1)	1359 (7.6)	13907 (77.9)	2032(11.4)		
Age yr						
[45-50[	72 (13.2)	202 (14.9)	388 (2.8)	0 (0.0)		
[50-55[	82 (15.1)	245 (18.0)	2387 (17.2)	0 (0.0)		
[55-60[	105 (19.3)	301 (22.1)	4067 (29.2)	353 (17.4)	<0.001	
[60-65[	133 (24.5)	277 (20.4)	3778 (27.2)	588 (28.9)		
>= 65	152 (27.9)	334 (24.6)	3287 (23.6)	1091 (53.7)		
Height cm (MV=543)						
<157	113 (21.2)	302 (23.0)	2899 (21.5)	534 (27.1)		
[157-161[	175 (32.8)	398 (30.4)	4099 (30.3)	608 (30.9)	0.005	0.067
[161-166[	125 (23.3)	323 (24.6)	3256 (24.2)	435 (22.1)		
>=166	121 (22.7)	288 (22.0)	3231 (24.0)	392 (19.9)		
BMI kg/m² (MV=732)						
< 25	249 (47.1)	699 (54.0)	7904 (59.3)	1073 (55.2)		
25 - 30	177 (33.5)	389 (30.1)	3728 (27.9)	579 (29.7)	0.001	<0.001
>=30	103 (19.4)	206 (15.9)	1710 (12.8)	293 (15.1)		
Marital status (MV=406)						
In a relationship	313 (59.4)	818 (62.0)	8747 (64.3)	1237 (62.4)		
Single	65 (12.3)	181 (13.7)	1702 (12.5)	214 (10.8)	0.130	0.450
Separated/Divorced/Widow	149 (28.3)	320 (24.3)	3158 (23.2)	532 (26.8)		
Revenues (MV=1741)						
<45€ - <1500€	77 (16.4)	173 (14.3)	1210 (9.6)	195 (10.7)		
1500€ - <2180€	171 (36.2)	427 (35.3)	3746 (29.7)	580 (31.9)	<0.001	<0.001
2180€ - 4200€ +	223 (47.4)	609 (50.4)	7647 (60.7)	1043 (57.4)		
Education (MV=347)						
No education/Primary education	214 (40.3)	531 (39.9)	4431 (32.4)	669 (33.8)		
High school degree	95 (17.9)	236 (17.7)	2540 (18.6)	342 (17.3)	<0.001	<0.001
Bachelor's degree	159 (29.9)	414 (31.1)	4723 (34.6)	681 (34.4)		
Master's Degree/PhD/Others	63 (11.9)	151 (11.3)	1959 (14.4)	287 (14.5)		
Physical activity (MV=1013)						
Inactive	118 (23.5)	300 (23.8)	2519 (19.1)	323 (17.1)		
Moderately active	204 (40.6)	530 (42.0)	5744 (43.6)	768 (40.7)	<0.001	0.104
Very active	180 (35.9)	433 (34.2)	4912 (37.3)	798 (42.2)		
Alcohol consumption (MV=2564)						
No consumption	107 (23.7)	226 (19.7)	2075 (17.4)	301 (17.6)		
Moderate consumption	310 (68.7)	815 (70.9)	8804 (73.5)	1244 (72.5)	0.003	0.074
Unsafe consumption	34 (7.6)	108 (9.4)	1084 (9.1)	170 (9.9)		
Smoking status (MV=830)						
Never	272 (52.9)	661 (51.0)	6810 (51.4)	1123 (57.9)		
Past	63 (12.3)	209 (16.1)	1626 (12.2)	142 (7.3)	<0.001	0.042
Current	179 (34.8)	426 (32.9)	4827 (36.4)	674 (34.8)		

Appendix 6: follows

Characteristics	Age at menopause				P for trend	p* for trend
	Premature	Early	Normal	Late		
Diabetes						
No	511 (93.9)	1319 (97.1)	13609 (97.9)	1975 (97.2)	0.001	<0.001
Yes	33 (6.1)	40 (2.9)	298 (2.1)	57 (2.8)		
Hypertension (MV=14)						
No	302 (55.5)	864 (63.7)	8917 (64.2)	1123 (55.3)	0.019	<0.001
Yes	242 (44.5)	493 (36.3)	4980 (35.8)	907 (44.7)		
Hypercholesterolemia (MV=14)						
No	298 (54.8)	834 (61.5)	8232 (59.2)	1108 (54.5)	0.031	0.053
Yes	246 (45.2)	523 (38.5)	5664 (40.8)	923 (45.5)		
Depression (MV=236)						
No	377 (70.5)	933 (69.4)	10349 (75.4)	1562 (78.1)	<0.001	<0.001
Yes	158 (29.5)	411 (30.6)	3377 (24.6)	439 (21.9)		
MMSE (MV=103)						
>=29	236 (43.4)	625 (46.2)	7292 (52.8)	1027 (50.8)		
28	120 (22.1)	285 (21.1)	2659 (19.2)	391 (19.3)	<0.001	<0.001
<28	188 (34.5)	443 (32.7)	3867 (28.0)	606 (29.9)		
Respiratory affections (MV=242)						
No	471 (87.5)	1200 (89.3)	12535 (91.4)	1841 (91.9)	<0.001	<0.001
Yes	67 (12.5)	144 (10.7)	1180 (8.6)	162 (8.1)		
Renal affections (MV=282)						
No	531 (99.6)	1328 (99.1)	13632 (99.6)	1991 (99.7)	0.143	0.136
Yes	2 (0.4)	12 (0.9)	57 (0.4)	7 (0.3)		
Cardiovascular affections (MV=260)						
No	510 (94.8)	1303 (97.2)	13443 (98.0)	1949 (97.8)	<0.001	<0.001
Yes	28 (5.2)	37 (2.8)	268 (2.0)	44 (2.2)		
Arthritis (MV=477)						
No	515 (98.1)	1300 (97.7)	13276 (98.1)	1939 (98.2)	0.478	0.404
Yes	10 (1.9)	30 (2.3)	260 (1.9)	35 (1.8)		
Cancer of ovaries and uterus						
No	498 (91.5)	1323 (97.4)	13768 (99.0)	1985 (97.7)	<0.001	<0.001
Yes	46 (8.5)	36 (2.6)	139 (1.0)	47 (2.3)		

MV : missing values
BMI : body mass index
*** : adjusted for age**

Appendix 7: Baseline characteristics and their association with time since onset of menopause

Characteristics	Time since onset of menopause				p for trend	p* for trend
	≤4.5	]4.5-9.5]	]9.5-14]	>14		
N (%)	4507 (25.3)	4302 (24.1)	4655 (26.1)	4378 (24.5)		
Age yr						
[45-50[	494 (11.0)	118 (2.6)	33 (0.7)	17 (0.4)		
[50-55[	1980 (43.9)	510 (11.9)	160 (3.4)	64 (1.5)		
[55-60[	1741 (38.6)	1981 (46.1)	786 (16.9)	318 (7.2)	<0.001	
[60-65[	229 (5.1)	1435 (33.4)	2085 (44.8)	1027 (23.5)		
>= 65	63 (1.4)	258 (6.0)	1591 (34.2)	2952 (67.4)		
Height cm (MV=543)						
<157	677 (15.5)	876 (21.0)	1104 (24.5)	1191 (27.9)		
[157-161[	1199 (27.5)	1249 (30.0)	1418 (31.4)	1414 (33.2)	<0.001	<0.001
[161-166[	1113 (25.6)	1025 (24.6)	1047 (23.2)	954 (22.4)		
>=166	1367 (31.4)	1016 (24.4)	945 (20.9)	704 (16.5)		
BMI kg/m² (MV=732)						
< 25	2662 (61.7)	2444 (59.4)	2573 (57.7)	2246 (53.3)		
25 - 30	1080 (25.0)	1125 (27.3)	1321 (29.6)	1347 (31.9)	<0.001	0.005
>=30	573 (13.3)	548 (13.3)	567 (12.7)	624 (14.8)		
Marital status (MV=406)						
In a relationship	2822 (63.8)	2651 (63.0)	2928 (64.3)	2714 (63.8)		
Single	679 (15.3)	560 (13.3)	522 (11.5)	401 (9.4)	<0.001	0.511
Separated/Divorced/Widow	925 (20.9)	997 (23.7)	1099 (24.2)	1138 (26.8)		

Appendix 7: follows

Characteristics	Time since onset of menopause				p for trend	p* for trend
	≤4.5	]4.5-9.5]	]9.5-14]	>14		
Revenues (MV=1741)						
<45€ - <1500€	420 (10.2)	386 (9.8)	401 (9.6)	448 (11.5)		
1500€ - <2180€	1076 (26.2)	1190 (30.2)	1341 (32.0)	1317 (34.1)	<0.001	<0.001
2180€ - 4200€ +	2616 (63.6)	2348 (59.8)	2455 (58.4)	2103 (54.4)		
Education (MV=347)						
No education/Primary education	1281 (28.9)	1322 (31.3)	1550 (34.0)	1692 (39.6)		
High school degree	785 (17.6)	770 (18.3)	882 (19.4)	776 (18.1)	<0.001	<0.001
Bachelor's degree	1680 (37.9)	1551 (36.7)	1481 (32.5)	1265 (29.6)		
Master's Degree/PhD/Others	693 (15.6)	578 (13.7)	644 (14.1)	545 (12.7)		
Physical activity (MV=1013)						
Inactive	997 (23.0)	857 (20.9)	762 (17.5)	644 (16.0)		
Moderately active	2001 (46.1)	1835 (44.7)	1775 (40.7)	1635 (40.6)	<0.001	0.161
Very active	1338 (30.9)	1413 (34.4)	1823 (41.8)	1749 (43.4)		
Alcohol consumption (MV=2564)						
No consumption	693 (17.7)	657 (17.8)	716 (18.0)	643 (17.5)		
Moderate consumption	2942 (75.0)	2717 (73.3)	2872 (72.1)	2642 (72.0)	<0.001	0.142
Unsafe consumption	289 (7.3)	328 (8.9)	392 (9.9)	387 (10.5)		
Smoking status (MV=830)						
Never	2074 (48.2)	2024 (49.1)	2376 (53.7)	2392 (57.4)		
Past	696 (16.2)	545 (13.2)	428 (9.7)	371 (8.9)	<0.001	0.051
Current	1534 (35.6)	1552 (37.7)	1619 (36.6)	1401 (33.7)		
Diabetes						
No	4454 (98.8)	4199 (97.6)	4539 (97.5)	4222 (96.4)	<0.001	<0.001
Yes	53 (1.2)	103 (2.4)	116 (2.5)	156 (3.6)		
Hypertension (MV=14)						
No	3313 (73.6)	2911 (67.7)	2760 (59.3)	2222 (50.8)	<0.001	<0.001
Yes	1191 (26.4)	1388 (32.3)	1893 (40.7)	2150 (49.2)		
Hypercholesterolemia (MV=14)						
No	3029 (67.3)	2549 (59.3)	2603 (55.9)	2291 (52.4)	<0.001	0.250
Yes	1475 (32.7)	1750 (40.7)	2050 (44.1)	2081 (47.6)		
Depression (MV=236)						
No	3355 (75.7)	3158 (74.2)	3504 (76.1)	3204 (74.3)	0.444	0.007
Yes	1078 (24.3)	1097 (25.8)	1102 (23.9)	1108 (25.7)		
MMSE (MV=103)						
>=29	2411 (53.8)	2276 (53.2)	2382 (51.5)	2111 (48.5)		
28	819 (18.2)	839 (19.6)	924 (20.0)	873 (20.1)	<0.001	<0.001
<28	1255 (28.0)	1160 (27.2)	1319 (28.5)	1370 (31.4)		
Respiratory affections (MV=242)						
No	4042 (91.0)	3866 (91.1)	4211 (91.5)	3928 (91.0)	0.800	0.163
Yes	398 (9.0)	379 (8.9)	389 (8.5)	387 (9.0)		
Renal affections (MV=282)						
No	4416 (99.8)	4217 (99.5)	4575 (99.6)	4274 (99.4)	0.008	0.037
Yes	11 (0.2)	19 (0.5)	20 (0.4)	28 (0.6)		
Cardiovascular affections (MV=260)						
No	4391 (99.0)	4148 (97.8)	4507 (98.0)	4159 (96.6)	<0.001	<0.001
Yes	46 (1.0)	94 (2.2)	92 (2.0)	145 (3.4)		
Arthritis (MV=477)						
No	4310 (98.3)	4100 (97.7)	4476 (98.5)	4144 (97.8)	0.476	0.472
Yes	76 (1.7)	96 (2.3)	69 (1.5)	94 (2.2)		
Cancer of ovaries and uterus						
No	4448 (98.7)	4239 (98.5)	4602 (98.9)	4285 (97.9)	0.011	<0.001
Yes	59 (1.3)	63 (1.5)	53 (1.1)	93 (2.1)		

MV : missing values
BMI : body mass index
*** : adjusted for age**

Appendix 8: Baseline characteristics and their association with duration of reproductive life span

Characteristics	Duration of reproductive life span				p for trend	p* for trend
	<35	[35-38[	[38-41[	>= 41		
N (%)	4016 (23.7)	3865 (22.8)	4788 (28.2)	4292 (25.3)		
Age yr						
[45-50[	482 (12.0)	123 (3.2)	16 (0.3)	0 (0.0)		
[50-55[	769 (19.2)	841 (21.8)	795 (16.6)	155 (3.6)		
[55-60[	961 (23.9)	1063 (27.4)	1466 (30.6)	1131 (26.4)	<0.001	
[60-65[	836 (20.8)	968 (25.1)	1394 (29.2)	1325 (30.9)		
>= 65	968 (24.1)	870 (22.5)	1117 (23.3)	1681 (39.1)		
Height cm (MV=521)						
<157	789 (20.2)	738 (19.8)	1044 (22.5)	1074 (25.8)		
[157-161[	1188 (30.5)	1113 (29.8)	1420 (30.6)	1305 (31.3)	<0.001	0.004
[161-166[	950 (24.4)	933 (25.0)	1093 (23.5)	979 (23.5)		
>=166	971 (24.9)	949 (25.4)	1087 (23.4)	807 (19.4)		
BMI kg/m² (MV=702)						
< 25	2260 (58.6)	2255 (61.0)	2699 (58.8)	2251 (54.7)		
25 - 30	1088 (28.2)	1001 (27.1)	1284 (28.0)	1246 (30.2)	<0.001	0.001
>=30	508 (13.2)	438 (11.9)	609 (13.2)	620 (15.1)		
Marital status (MV=387)						
In a relationship	2394 (61.3)	2421 (64.1)	3061 (65.3)	2735 (65.1)		
Single	545 (14.0)	493 (13.0)	557 (11.9)	434 (10.3)	<0.001	0.006
Separated/Divorced/Widow	963 (24.7)	866 (22.9)	1069 (22.8)	1036 (24.6)		
Revenues (MV=1621)						
<45€ - <1500€	483 (13.5)	332 (9.5)	366 (8.3)	339 (8.7)		
1500€ - <2180€	1228 (34.3)	1049 (29.8)	1228 (28.2)	1171 (30.2)	<0.001	<0.001
2180€ - 4200€ +	1872 (52.2)	2136 (60.7)	2767 (63.5)	2369 (61.1)		
Education (MV=329)						
No education/Primary education	1497 (38.1)	1208 (31.8)	1453 (30.9)	1284 (30.5)		
High school degree	688 (17.5)	688 (18.1)	911 (19.4)	778 (18.5)	<0.001	<0.001
Bachelor's degree	1265 (32.2)	1346 (35.5)	1619 (34.4)	1530 (36.4)		
Master's Degree/PhD/Others	477 (12.2)	554 (14.6)	719 (15.3)	615 (14.6)		
Physical activity (MV=923)						
Inactive	843 (22.3)	715 (19.5)	844 (18.5)	681 (16.8)		
Moderately active	1609 (42.8)	1620 (44.1)	1984 (43.6)	1688 (41.7)	<0.001	0.004
Very active	1312 (34.9)	1338 (36.4)	1726 (37.9)	1678 (41.5)		
Alcohol consumption (MV=2367)						
No consumption	659 (19.5)	590 (17.7)	669 (16.1)	640 (17.1)		
Moderate consumption	2433 (71.8)	2435 (73.3)	3080 (74.2)	2750 (73.8)	0.008	0.247
Unsafe consumption	296 (8.7)	300 (9.0)	404 (9.7)	338 (9.1)		
Smoking status (MV=780)						
Never	1900 (49.7)	1822 (49.6)	2400 (52.4)	2282 (55.6)		
Past	588 (15.3)	502 (13.7)	519 (11.4)	347 (8.4)	<0.001	<0.001
Current	1339 (35.0)	1346 (36.7)	1658 (36.2)	1478 (36.0)		
Diabetes						
No	3911 (97.4)	3777 (97.7)	4699 (98.1)	4175 (97.3)	0.924	0.168
Yes	105 (2.6)	88 (2.3)	89 (1.9)	117 (2.7)		
Hypertension (MV=13)						
No	2585 (64.4)	2520 (65.2)	3061 (64.0)	2502 (58.3)	<0.001	0.458
Yes	1428 (35.6)	1343 (34.8)	1722 (36.0)	1787 (41.7)		
Hypercholesterolemia (MV=11)						
No	2441 (60.8)	2326 (60.2)	2802 (58.5)	2411 (56.2)	<0.001	0.599
Yes	1572 (39.2)	1536 (39.8)	1984 (41.5)	1878 (43.8)		
Depression (MV=217)						
No	2879 (72.6)	2884 (75.6)	3585 (75.8)	3242 (76.5)	<0.001	0.001
Yes	1086 (27.4)	929 (24.4)	1143 (24.2)	996 (23.5)		
MMSE (MV=101)						
>=29	1886 (47.2)	2053 (53.4)	2622 (55.3)	2269 (53.1)		
28	835 (20.9)	742 (19.3)	894 (18.8)	842 (19.6)	<0.001	<0.001
<28	1273 (31.9)	1051 (27.3)	1228 (25.9)	1165 (27.3)		
Respiratory affections (MV=227)						
No	3577 (90.3)	3495 (91.6)	4306 (91.1)	3878 (91.6)	0.093	0.197
Yes	383 (9.7)	320 (8.4)	420 (8.9)	355 (8.4)		
Renal affections (MV=258)						
No	3939 (99.5)	3785 (99.6)	4697 (99.5)	4210 (99.6)	0.412	0.358
Yes	20 (0.5)	15 (0.4)	22 (0.5)	15 (0.4)		

Appendix 8: follows

Characteristics	Duration of reproductive life span				p for trend	p* for trend
	<35	[35-38[	[38-41[	>= 41		
Cardiovascular affections (MV=243)						
No	3844 (97.1)	3737 (98.0)	4650 (98.4)	4132 (97.9)	0.006	<0.001
Yes	115 (2.9)	76 (2.0)	74 (1.6)	90 (2.1)		
Arthritis (MV=449)						
No	3835 (98.0)	3686 (98.1)	4563 (97.9)	4112 (98.3)	0.431	0.355
Yes	79 (2.0)	70 (1.9)	96 (2.1)	71 (1.7)		
Cancer of ovaries and uterus						
No	3911 (97.4)	3827 (99.0)	4742 (99.0)	4227 (98.5)	<0.001	0.001
Yes	105 (2.6)	38 (1.0)	46 (1.0)	65 (1.5)		

MV : missing values
BMI : body mass index
*** : adjusted for age**

Appendix 9: Baseline characteristics and their association with oral contraceptive pills

Characteristics	Oral contraceptive pills			P value	p* value
	Never	Past	Current		
N (%)	2499 (10.8)	19879 (86.2)	682 (3.0)		
Age yr					
[45-50[	244 (9.8)	3746 (18.8)	518 (76.0)		
[50-55[	322 (12.9)	4244 (21.4)	155 (22.7)		
[55-60[	411 (16.4)	4376 (22.0)	9 (1.3)	<0.001	
[60-65[	572 (22.9)	3939 (19.8)	0 (0.0)		
>= 65	950 (38.0)	3574 (18.0)	0 (0.0)		
Height cm (MV=720)					
<157	625 (25.8)	3611 (18.8)	85 (12.7)		
[157-161[	788 (32.5)	5543 (28.8)	161 (24.1)	<0.001	<0.001
[161-166[	516 (21.3)	4801 (25.0)	186 (27.9)		
>=166	497 (20.4)	5291 (27.4)	236 (35.3)		
BMI kg/m² (MV=959)					
< 25	1294 (54.0)	11533 (60.5)	429 (64.8)		
25 - 30	703 (29.3)	5098 (26.8)	155 (23.4)	<0.001	<0.001
>=30	400 (16.7)	2411 (12.7)	78 (11.8)		
Marital status (MV=498)					
In a relationship	1451 (59.5)	12469 (64.0)	455 (68.5)		
Single	458 (18.7)	2641 (13.6)	107 (16.1)	<0.001	<0.001
Separated/Divorced/Widow	531 (21.8)	4348 (22.4)	102 (15.4)		
Revenues (MV=2069)					
<45€ - <1500€	347 (16.0)	1636 (9.0)	41 (6.6)		
1500€ - <2180€	769 (35.4)	5053 (27.8)	145 (23.3)	<0.001	<0.001
2180€ - 4200€ +	1055 (48.6)	11508 (63.2)	437 (70.1)		
Education (MV=394)					
No education/Primary education	966 (39.7)	5480 (28.0)	132 (19.7)		
High school degree	434 (17.7)	3507 (17.9)	104 (15.5)	<0.001	<0.001
Bachelor's degree	702 (28.9)	7372 (37.7)	297 (44.3)		
Master's Degree/PhD/Others	331 (13.7)	3204 (16.4)	137 (20.5)		
Physical activity (MV=1077)					
Inactive	482 (20.7)	4049 (21.3)	188 (28.2)		
Moderately active	956 (41.1)	8493 (44.7)	306 (46.0)	<0.001	0.093
Very active	886 (38.2)	6451 (34.0)	172 (25.8)		
Alcohol consumption (MV=3130)					
No consumption	440 (22.2)	3056 (17.6)	110 (18.2)		
Moderate consumption	1380 (69.5)	12749 (73.5)	462 (76.5)	<0.001	<0.001
Unsafe consumption	165 (8.3)	1536 (8.9)	32 (5.3)		
Smoking status (MV=1028)					
Never	1612 (67.5)	9260 (48.8)	339 (52.3)		
Past	208 (8.7)	2651 (14.0)	94 (14.5)	<0.001	<0.001
Current	568 (23.8)	7085 (37.2)	215 (33.2)		

Appendix 9: follows

Characteristics	Oral contraceptive pills			P value	p* value
	Never	Past	Current		
Diabetes					
No	2420 (96.8)	19514 (98.2)	675 (99.0)	<0.001	0.017
Yes	79 (3.2)	365 (1.8)	7 (1.0)		
Hypertension (MV=14)					
No	1518 (60.8)	13696 (68.9)	522 (76.5)	<0.001	<0.001
Yes	978 (39.2)	6172 (31.1)	160 (23.5)		
Hypercholesterolemia (MV=13)					
No	1472 (59.0)	13075 (65.8)	567 (83.3)	<0.001	0.230
Yes	1025 (41.0)	6794 (34.2)	114 (16.7)		
Depression (MV=307)					
No	1966 (79.6)	14840 (75.7)	528 (78.2)	<0.001	<0.001
Yes	503 (20.4)	4769 (24.3)	147 (21.8)		
MMSE (MV=133)					
>=29	1183 (47.6)	10835 (54.8)	392 (57.7)		
28	468 (18.9)	3723 (18.8)	149 (21.9)	<0.001	<0.001
<28	832 (33.5)	5206 (26.4)	139 (20.4)		
Respiratory affections (MV=313)					
No	2252 (91.2)	17831 (91.0)	613 (90.8)	0.909	0.749
Yes	217 (8.8)	1772 (9.0)	62 (9.2)		
Renal affections (MV=350)					
No	2454 (99.5)	19493 (99.6)	675 (99.6)	0.675	0.730
Yes	12 (0.5)	73 (0.4)	3 (0.4)		
Cardiovascular affections (MV=326)					
No	2413 (97.8)	19246 (98.3)	676 (99.9)	0.001	0.110
Yes	55 (2.2)	343 (1.7)	1 (0.1)		
Arthritis (MV=581)					
No	2394 (98.2)	19027 (98.2)	656 (98.1)	0.926	0.535
Yes	45 (1.8)	344 (1.8)	13 (1.9)		
Cancer of ovaries and uterus					
No	2462 (98.5)	19631 (98.8)	677 (99.3)	0.283	0.626
Yes	37 (1.5)	248 (1.2)	5 (0.7)		

MV : missing values
BMI : body mass index
*** : adjusted for age**

Appendix 10: Baseline characteristics and their association with post-menopausal hormonal therapy

Characteristics	Post-menopausal hormonal therapy			p value	p* value
	Never	Past	Current		
N (%)	15068 (85.0)	365 (2.1)	2287 (12.9)		
Age yr					
[45-50[	608 (4.0)	12 (3.3)	128 (5.5)		
[50-55[	2269 (15.1)	42 (11.5)	415 (18.2)		
[55-60[	4006 (26.6)	56 (15.3)	670 (29.3)	<0.001	
[60-65[	4035 (26.8)	97 (26.6)	569 (24.9)		
>= 65	4150 (27.5)	158 (43.3)	505 (22.1)		
Height cm (MV=537)					
<157	3280 (22.5)	92 (25.8)	433 (19.5)		
[157-161[	4488 (30.7)	94 (26.3)	646 (29.1)	<0.001	0.024
[161-166[	3462 (23.7)	92 (25.8)	554 (24.9)		
>=166	3375 (23.1)	79 (22.1)	588 (26.5)		
BMI kg/m² (MV=720)					
< 25	8165 (56.5)	231 (65.1)	1496 (68.1)		
25 - 30	4197 (29.1)	94 (26.4)	537 (24.4)	<0.001	<0.001
>=30	2085 (14.4)	30 (8.5)	165 (7.5)		
Marital status (MV=396)					
In a relationship	9353 (63.5)	234 (66.5)	1472 (65.7)		
Single	1838 (12.5)	37 (10.5)	262 (11.7)	0.218	0.181
Separated/Divorced/Widow	3542 (24.0)	81 (23.0)	505 (22.6)		
Revenues (MV=1726)					
<45€ - <1500€	1466 (10.8)	18 (5.5)	159 (7.7)		
1500€ - <2180€	4242 (31.2)	121 (36.7)	505 (24.4)	<0.001	<0.001
2180€ - 4200€ +	7888 (58.0)	190 (57.8)	1405 (67.9)		

Appendix 10: follows

Characteristics	Post-menopausal hormonal therapy			p value	p* value
	Never	Past	Current		
Education (MV=342)					
No education/Primary education	5058 (34.2)	125 (35.2)	564 (25.1)	<0.001	<0.001
High school degree	2716 (18.4)	63 (17.8)	418 (18.6)		
Bachelor's degree	5037 (34.1)	120 (33.8)	824 (36.7)		
Master's Degree/PhD/Others	1967 (13.3)	47 (13.2)	439 (19.6)		
Physical activity (MV=990)					
Inactive	2841 (20.0)	48 (14.1)	379 (17.3)	0.002	<0.001
Moderately active	6122 (43.1)	156 (45.8)	947 (43.2)		
Very active	5236 (36.9)	137 (40.1)	864 (39.5)		
Alcohol consumption (MV=2525)					
No consumption	2367 (18.4)	57 (17.7)	292 (14.5)	0.001	<0.001
Moderate consumption	9334 (72.6)	233 (72.1)	1524 (75.5)		
Unsafe consumption	1154 (9.0)	33 (10.2)	201 (10.0)		
Smoking status (MV=844)					
Never	7526 (52.4)	178 (52.7)	1077 (49.4)	<0.001	0.001
Past	1765 (12.3)	24 (7.1)	252 (11.6)		
Current	5068 (35.3)	136 (40.2)	850 (39.0)		
Diabetes					
No	14682 (97.4)	359 (98.4)	2260 (98.8)	<0.001	<0.001
Yes	386 (2.6)	6 (1.6)	27 (1.2)		
Hypertension (MV=13)					
No	9342 (62.0)	227 (62.2)	1619 (70.8)	<0.001	<0.001
Yes	5713 (38.0)	138 (37.8)	668 (29.2)		
Hypercholesterolemia (MV=13)					
No	8706 (57.8)	228 (62.5)	1525 (66.7)	<0.001	<0.001
Yes	6350 (42.2)	137 (37.5)	761 (33.3)		
Depression (MV=234)					
No	11225 (75.5)	237 (65.7)	1656 (73.4)	<0.001	<0.001
Yes	3644 (24.5)	124 (34.3)	600 (26.6)		
MMSE (MV=106)					
>=29	7737 (51.6)	192 (53.0)	1225 (54.0)	0.109	0.122
28	2921 (19.5)	69 (19.1)	450 (19.8)		
<28	4326 (28.9)	101 (27.9)	593 (26.2)		
Respiratory affections (MV=241)					
No	13542 (91.1)	327 (90.8)	2067 (91.4)	0..887	0.831
Yes	1316 (8.9)	33 (9.2)	194 (8.6)		
Renal affections (MV=278)					
No	14771 (99.6)	357 (98.9)	2238 (99.6)	0.145	0.177
Yes	63 (0.4)	4 (1.1)	9 (0.4)		
Cardiovascular affections (MV=256)					
No	14507 (97.7)	353 (97.8)	2232 (98.9)	0.003	0.005
Yes	338 (2.3)	8 (2.2)	26 (1.1)		
Arthritis (MV=470)					
No	14385 (98.1)	351 (98.9)	2186 (98.0)	0.522	0.477
Yes	279 (1.9)	4 (1.1)	45 (2.0)		
Cancer of ovaries and uterus					
No	14837 (98.5)	361 (98.9)	2257 (98.7)	0.587	0.554
Yes	231 (1.5)	4 (1.1)	30 (1.3)		

MV : missing values
BMI : body mass index
*** : adjusted for age**

Appendix 11: Summary of association between baseline characteristics and hormonal exposures

Baseline characteristics	Age at menarche	Parity	Age at first pregnancy	Menopause	Type of menopause*	Age at menopause*	Time since onset of menopause*	Duration of reproductive life span*	Oral contraceptive pills	Post-menopausal hormonal therapy*
Height	+	+	+	-			-	-	+	+
BMI	-	+	-		+	-	+	+	-	-
Marital status (relationship)	-	+	-		+			+	+	
Revenues	-	+	+	-	-	+	-	+	+	+
Education	-	-	+	-	-	+	-	+	+	+
Physical activity		+						+	-	+
Alcohol consumption (unsafe)	+		+						-	+
Smoking status (current)	-	-	+	+	-	-		+	+	+
Diabetes	-	+	-		+	-	+		-	-
Hypertension	-	+	-		+	+	+		-	-
Hypercholesterolemia	-		-	+	+		+			-
Depression	-	-	-	+	+	-	+	-	-	-
MMSE	-		+	-	-	+	-	+	+	+
Respiratory affections			-		+	-				
Renal affections				+			+			
Cardiovascular affections			-	+	+	-	+	-		-
Athritis			-							
Cancer of the ovaries/uterus			-	+	+	-	+	-		

*** among postmenopausal women** **+: positive association** **-: negative association**

Appendix 12: Multinomial logistic regression between reproductive life characteristics and walking speed categories adjusted for age, centre and confounders in all women (Model 3)

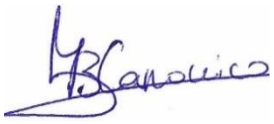
Characteristics of reproductive life	Walking speed (cm/s)										
	Quartile 4		Quartile 3			Quartile 2			Quartile 1		P*
	N		OR (95%CI)	p	N	OR (95%CI)	p	N	OR (95%CI)	p	
Age at menarche											
≥12	2161	2340	1.00 (reference)		2474	1.00 (reference)		2509	1.00 (reference)		
]12-13]	1450	1407	0.97 (0.88; 1.07)	0.567	1414	0.99 (0.89; 1.09)	0.823	1247	0.95 (0.85; 1.06)	0.360	0.678
]13-14]	1231	1174	0.94 (0.84; 1.04)	0.219	1100	0.89 (0.80; 0.99)	0.029	1006	0.86 (0.77; 0.97)	0.012	0.015
> 14	1059	924	0.86 (0.77; 0.97)	0.010	936	0.89 (0.79; 0.99)	0.039	905	0.84 (0.74: 0.95)	0.004	0.014
p for linear trend				0.046			0.048			0.002	
Nulliparous											
No	5215	5221	1.00 (reference)		5266	1.00 (reference)		5195	1.00 (reference)		
Yes	578	554	0.98 (0.83; 1.15)	0.777	574	1.05 (0.88; 1.24)	0.598	478	1.06 (0.88; 1.28)	0.520	0.319
Parity											
0	578	554			574			478			
1	926	1040	1.00 (reference)		1119	1.00 (reference)		1054	1.00 (reference)		
2	2497	2583	0.95 (0.85; 1.06)	0.363	2680	0.90 (0.81; 1.01)	0.081	2536	0.91 (0.81; 1.03)	0.126	0.108
≥3	1792	1598	0.83 (0.73; 0.94)	0.004	1467	0.71 (0.63; 0.81)	<0.001	1605	0.77 (0.68; 0.89)	<0.001	<0.001
p for linear trend				<0.001			<0.001			<0.001	
Age at first pregnancy											
<24 years	1012	1268	1.00 (reference)		1434	1.00 (reference)		1900	1.00 (reference)		
[24-27[years	1399	1294	0.84 (0.74; 0.95)	0.004	1400	0.90 (0.80; 1.02)	0.094	1274	0.77 (0.68; 0.87)	<0.001	<0.001
[27-30[years	1282	1200	0.88 (0.78; 0.99)	0.047	1084	0.82 (0.72; 0.94)	0.003	941	0.75 (0.65; 0.85)	<0.001	<0.001
≥30years	1504	1440	0.87 (0.76; 0.99)	0.036	1326	0.83 (0.72; 0.94)	0.005	1041	0.70 (0.61; 0.81)	<0.001	<0.001
p for linear trend				0.163			0.012			<0.001	

*** : p of ordinal regression**

Appendix 13: Multinomial logistic regression between reproductive life characteristics and walking speed categories adjusted for age, centre and confounders in menopaused women (Model 3)

Characteristics of reproductive life	Walking speed (cm/s)										P*
	Quartile 4	Quartile 3			Quartile 2			Quartile 1			
	N=	N=	OR (95%CI)	p	N=	OR (95%CI)	p	N=	OR (95%CI)	p	
Age at menarche											
≤12	1647	1800	1.00 (reference)		1907	1.00 (reference)		1970	1.00 (reference)		
]12-13]	1088	1046	0.96 (0.86; 1.08)	0.531	1056	0.98 (0.87; 1.11)	0.764	919	0.89 (0.78; 1.01)	0.077	0.225
]13-14]	884	863	0.95 (0.84; 1.08)	0.456	821	0.91 (0.80; 1.04)	0.151	770	0.87 (0.76; 0.99)	0.048	0.073
> 14	758	682	0.87 (0.76; 0.99)	0.041	656	0.85 (0.74; 0.97)	0.019	686	0.83 (0.71; 0.96)	0.010	0.018
p for linear trend				0.153			0.058			0.012	
Nulliparous											
No	3858	3908	1.00 (reference)		3941	1.00 (reference)		3989	1.00 (reference)		
Yes	430	415	1.02 (0.84; 1.24)	0.877	418	1.09 (0.89; 1.33)	0.398	367	1.23 (0.98; 1.53)	0.069	0.031
Parity											
0	430	415			418			367			
1	726	809	1.00 (reference)		882	1.00 (reference)		808	1.00 (reference)		
2	1844	1917	0.95 (0.84; 1.09)	0.461	1974	0.88 (0.77; 1.01)	0.060	1943	0.97 (0.85; 1.12)	0.726	0.555
≥3	1288	1182	0.87 (0.75; 1.01)	0.065	1085	0.72 (0.62; 0.84)	<0.001	1238	0.84 (0.72; 0.99)	0.032	0.005
p for linear trend				0.023			<0.001			0.013	
Age at first pregnancy											
<24 years	874	1104	1.00 (reference)		1245	1.00 (reference)		1624	1.00 (reference)		
[24-27[years	1091	1008	0.86 (0.75; 0.98)	0.025	1070	0.92 (0.80; 1.05)	0.196	994	0.79 (0.69; 0.91)	0.001	0.004
[27-30[years	873	803	0.90 (0.78; 1.04)	0.140	727	0.85 (0.73; 0.98)	0.030	659	0.80 (0.68; 0.94)	0.006	0.003
≥30years	1007	977	0.92 (0.79; 1.07)	0.258	881	0.86 (0.74; 1.00)	0.050	681	0.75 (0.64; 0.88)	0.001	<0.001
p for linear trend				0.543			0.098			0.002	
Type of menopause											
Natural	4063	3971	1.00 (reference)		4026	1.00 (reference)		3909	1.00 (reference)		
Artificial	513	636	1.21 (1.04; 1.39)	0.013	642	1.08 (0.93; 1.26)	0.297	751	1.14 (0.98; 1.34)	0.094	0.275
Age at menopause											
Not premature menopause	4315	4319	1.00 (reference)		4379	1.00 (reference)		4285	1.00 (reference)		
Premature menopause	107	125	1.14 (0.84; 1.56)	0.408	128	1.00 (0.73; 1.38)	0.984	184	1.22 (0.88; 1.68)	0.234	0.458
Time since onset of menopause											
≤4.5	1164	1146	1.00 (reference)		1114	1.00 (reference)		1083	1.00 (reference)		
]4.5-9.5]	992	1111	1.12 (0.98; 1.28)	0.105	1112	1.21 (1.05; 1.39)	0.009	1087	1.20 (1.03; 1.39)	0.021	0.007
]9.5-14]	1224	1121	0.87 (0.74; 1.02)	0.086	1150	0.98 (0.83; 1.15)	0.786	1160	1.02 (0.86; 1.22)	0.800	0.499
>14	1042	1066	0.89 (0.73; 1.08)	0.227	1131	1.06 (0.87; 1.30)	0.546	1139	1.07 (0.87; 1.32)	0.516	0.124
P for linear trend				0.110			0.609			0.686	

*** : p of ordinal regression**



Academic advisor

Olivier GRIMAUD

Professional advisor

Marianne CANONICO