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Clinical Research Article

Association of Hormonal Exposures With Grip Strength in Women >45 Years: Data From the CONSTANCES Cohort Study

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Abstract

Context: Although biological findings show that estrogens are beneficial for muscular mass maintenance and bone resorption inhibition, the association of hormonal exposure with physical performance are controversial.

Objective: We investigated the association of reproductive history and exogenous hormone use with hand-grip strength (GS) in women.

Methods: Using the data from the CONSTANCES French prospective population-based cohort study, we ran linear mixed models to investigate the association of reproductive history and exogenous hormones use with maximal GS in 37 976 women aged 45 to 69 years recruited between 2012 and 2020. We used multiple imputation by chained equations to control missing values and corrections for multiple testing.

Results: The mean age of women was 57.2 years. Mean GS was 26.6 kg. After adjustment for age and confounders, GS increased with age at menarche ($\beta_{+1\ year} = 0.14$; 95% CI, 0.10-0.17) and duration of breastfeeding ($\beta_{\text{for} \geq 10 \text{ months vs} < 5 \text{ months}} = 0.39$; 95% CI, 0.20-0.59; *P* for linear trend <.01). Compared to nonmenopausal women, postmenopausal women had significantly lower GS ($\beta = -0.78$; 95% CI, −0.98 to −0.58). GS was negatively associated with hormone therapy (HT) past use ($\beta = -0.25$; 95% CI, −0.42 to −0.07).

Conclusion: Our results suggested that menopausal transition was strongly associated with lower GS. However, despite our hypothesis, increased age at menarche and duration of breastfeeding were associated with higher GS and HT past users presented lower GS than HT never users. These findings could help identify women at high risk of poor physical performance.

Key Words: ovarian hormonal exposure, women, grip strength, mid-life and older adults, population-based cohort

Abbreviations: BMD, bone mineral density; GS, hand-grip strength; HSC, Health Screening Center; HT, hormone therapy; MMSE, Mini-Mental State Examination; WHQ, lifestyle, health behaviors, socio-professional status, lifetime employment history, and women's health questionnaire.

Given increased life expectancy across the world, healthy aging has become a major public health issue. Physiological aging processes are characterized by a decline in physical performance associated with negative outcomes, such as frailty, hospitalizations, disability, and death [1-5]. The integrity of musculoskeletal and connective tissues, together with muscle strength, contribute to maintenance of mobility and physical performance [6]. Muscle strength can be easily evaluated through measures of hand-grip strength (GS) [3]. GS is a reliable approximation of body muscle strength [5], strongly related to lower extremity muscle power, and informs a sarcopenia diagnosis [7]. GS therefore represents a valuable tool for identifying individuals at high risk of physical limitations related to low muscle strength and thus facilitating early intervention.

Steroid sex hormones, including estrogens, progesterone, and androgens, play an important role in preserving bone mineral density (BMD) and muscle mass in women [8, 9]. In particular, the beneficial effects of estrogens has been hypothesized to explain, at least in part, differences in physical performances among women [10, 11]. This is supported by epidemiological studies showing decreased physical performance in menopausal compared to premenopausal women [12, 13]. In addition, women with artificial or premature menopause exhibit lower GS that women with natural menopause [13-19]. Alternatively, the association of hormonal supplementation with physical performance remains controversial [20-22]. Few studies have investigated the role of other reproductive history characteristics that represent proxies for endogenous hormonal exposure, such as age at menarche, parity, or breastfeeding [23-27]. This study aims to address this gap in the extant literature by investigating the association of characteristics of reproductive history and exogenous hormones use with GS in women, using baseline data from the CONSTANCES French prospective cohort study, the largest epidemiological study involving data with physical performance tests to date.

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Methods

Study Design and Population

We used data from the CONSTANCES study, a French prospective population-based cohort that gathered data between 2012 and 2020 on more than 220 000 participants aged 18 to 69 years from 16 regions [28, 29]. Eligible participants were randomly selected and the sample was representative of the French adult population based on age, gender, socioeconomic status, and region of residence. The sample was restricted to affiliates of the French General Social Security System (professionally active, unemployed, or retired) or their family members (if unemployed), therefore excluding agricultural and self-employed workers.

Eligible volunteers were asked to complete self-administered questionnaires on lifestyle, health behaviors, socio-professional status, lifetime employment history, and women's health (WHQ). Moreover, they attended 1 of 21 Health Screening Centers (HSCs) for a health check-up, collection of blood and urine samples, and an interview with a physician who completed a medical history questionnaire. In addition, participants aged 45 years and older benefited from a functional assessment by a neuropsychologist, including cognitive and physical tests (walking speed, GS, standing balance). Our analyses were restricted to women aged 45 years and older.

CONSTANCES was authorized by the French Data Protection Authority and was approved by the institutional review voard of the National Institute for Medical Research. All participants gave informed consent.

Hand-grip Strength Assessment

From 2012 to 2014, the hand-grip isometric force was measured using the JAMAR PLUS + Hand Dynamometer, based on a sealed hydraulic system and switched in June 2014 to the JAMAR PLUS + Digital Hand Dynamometer using electronic cells that increases the GS measures accuracy.

GS measures were taken in a standing position with the participant's preferred hand, while keeping the arm tight along the body and the forearm at a 90° angle. For both dynamometers, the handle was adjusted to the participant's hand size, to rest on the index second phalanx and following fingers. Participants were instructed to squeeze the handle as hard as possible for 2 seconds before releasing it. Three measures were taken with a one minute interval between them; the results are reported in kilograms as integer values.

Specific conditions for GS measurement included performing the test while seated, with the arm resting on a table, using the nonpreferred hand, too large hand size, and interruptions during the test. In addition, specific conditions included patients with self-reported arthrosis, sensory deficit (ie, visual acuity <5 in the better-sighted eye or hearing impairment mild to deaf), or a functional deficit (ie, joint prosthesis, disability, or paralysis).

Maximal GS is characterized by a small but significantly greater variability (SD, 5.7 kg) than mean GS (SD, 5.6 kg; $P < .01$). In addition, most of recent epidemiological studies on GS used maximal rather than a mean measure [12, 13, 17, 19, 20, 22, 27, 30, 31]. Therefore, in line with the existing literature and because of a higher statistical power to detect associations, we used maximal GS in our analyses [3].

Characteristics of Reproductive History and Exogenous Hormone Use

The WHQ permitted collection of baseline self-reported data regarding both characteristics of reproductive history and exogenous hormones. Age at menarche was considered to approach puberty and parity was defined as the total number of pregnancy outcomes after 22 weeks of amenorrhea including livebirths and stillbirths, both considered to define age at first birth. Breastfeeding status (never/ever) and the total lifetime duration of breastfeeding in months were assessed using information reported for each livebirth and computed as the sum of breastfeeding durations.

Menopausal status was assessed in several steps as described [32], using a hierarchical algorithm (Supplementary Fig. S1) [33]. Postmenopausal status was defined as 1 of the following criteria: self-reported postmenopausal status, age ≥60 years, personal history of bilateral oophorectomy or hysterectomy, current or past use of hormone therapy (HT), or cessation of menstrual periods for more than 1 year in absence of current contraception use. Women were classified as premenopausal if they: self-reported to be premenopausal or if they were pregnant, were currently breastfeeding, delivered a baby within 12 months before enrollment in the study, suffered from endometriosis, or were currently using contraception. Among nonmenopausal women, those who reported to be perimenopausal or had their last menstruation within the past 3 to 12 months were classified as perimenopausal [34]. Type of menopause was defined as natural or artificial (surgical or iatrogenic), whichever occurred first. Surgical menopause included a history of bilateral oophorectomy or hysterectomy. Iatrogenic menopause included women reporting a history of cancer requiring iatrogenic chemotherapy treatment over a 1-year interval around the declared age at menopause or if they self-reported an iatrogenic amenorrhea and provided information on the type of iatrogenic molecules. Age at menopause was self-reported. Reproductive lifetime duration was computed as the difference between age at menopause and age at menarche. Time since onset of menopause was calculated as the difference between age at enrollment and age at menopause.

Exogenous hormones included the contraceptive pill and HT. Pill use included oral contraception of any composition; the lifetime duration of pill use (in years) and the age at initiation were self-reported among lifetime users. HT included preparations containing estrogens alone or combined with progestogen, administered by oral or transdermal route (except vaginal treatments), or tibolone. For women who declared to be current HT users, age at current HT initiation was collected as the age at initiation of this specific treatment.

Covariates

Socioeconomic and demographic characteristics included: monthly household income (<€1500, €1500-2800, ≥€2800), education level (no education/primary education, high school degree, bachelor's or master's degree/doctoral degree/others), marital status (coupled, single, divorced, or widowed), and father's and mother's socio-professional category during the participant's adolescence (farmer, craftsman/trader/business owner, manager/executive/upper intellectual, intermediate profession, employee, manual worker, no occupation/other). Heavy physical labor was defined as carrying heavy

loads or degree of medium or high physical effort usually required at work.

During the physical examination, anthropometric characteristics (weight in kilograms, height in centimeters) and blood pressure were measured. Body mass index was calculated by dividing weight in kilograms by height in meters squared and was treated as a continuous variable. Silhouettes in childhood (aged 8 years) and at age 18 years were self-reported based on the Sorensen's 7 silhouettes figures and categorized as slim, normal, and overweight [35]. Hypertension was defined according to the World Health Organization criteria as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or use of antihypertensive drugs. Blood samples were collected for laboratory tests and were used to define hypercholesterolemia (low-density lipoprotein cholesterol ≥4.14 mmol/L or use of cholesterol-lowering drugs) and diabetes (history of diabetes or fasting blood glucose level ≥7 mmol/L). Cognition was assessed using the Mini-Mental State Examination (MMSE) score categorized in tertiles (<28, 28, ≥29), and depressive symptoms were identified using the Centre for Epidemiological Studies-Depression Scale based on a cutoff of ≥16.

Self-reported health-related behaviors included: smoking status (never, former, current smoker), alcohol consumption (abstinent, moderate [≤2 standard drinks/day], high [>2 standard drinks/day]), and extent of physical activity outside of work (score based on 3 questions about time spent walking or cycling, playing sports, tinkering, gardening, or doing housework; the score was categorized as inactive, moderate, or high). Medical history of cardio- and cerebrovascular (angina pectoris, myocardial infarction, stroke, lower limbs arteritis), respiratory (chronic bronchitis, emphysema, asthma), and rheumatological (inflammatory arthritis, osteoarthritis) diseases as well as a history of breast cancer, uterine, or ovarian cancer were collected during the medical interview.

Statistical Analysis

We excluded women who did not fill the WHQ or completed it more than 1 year before or after the GS measure, pregnant women or those who gave birth within 6 weeks, those with Parkinson disease, and women who attended HSCs during periods without neuropsychologists or dynamometers.

Multiple Imputation by Chained Equations was used to impute missing values of GS, exposures, and covariates [36]. Additional proxies of physical function and all the covariates described below were included in the multiple imputation model (Supplementary methods) [33]. We generated 16 imputed datasets; regression coefficients from each model were pooled according to Rubin's rules [37].

Age at menarche, age at first birth, reproductive lifetime duration, time since onset of menopause, age at contraceptive pill initiation, and age at current HT initiation were considered as continuous variables or classified in tertiles. Lifetime duration of breastfeeding was considered in tertiles only because of its skewed distribution. Menopausal status was used as a 2-level categorical variable, including nonmenopausal (pre- and perimenopausal) and postmenopausal women; perimenopausal women were then compared to premenopausal women. Among postmenopausal women, type of menopause was first categorized as natural or artificial and then as natural, iatrogenic, and surgical, and third as natural, iatrogenic, oophorectomy, and hysterectomy only. Age at menopause was considered as a continuous or categorical variable: premature (age <40 years), early (age 40-44 years), normal (age 45-55 years), late (age >55 years). Ordinal variables were used for parity (1, 2, ≥3) and lifetime duration of contraceptive pill use (<1, 1-5, 5 years and more). Contraceptive pill use was categorized as never/ever and HT use was classified as never/past/current use.

The associations between hormonal characteristics and GS were estimated using regression coefficients (β) and 95% CIs using linear mixed models with a random intercept for centers. Model 1 included each hormonal characteristic separately and was adjusted for age at the interview with the neuropsychologist, specific conditions for GS measures, and type of dynamometer. Model 2 was further adjusted for different sets of confounders for puberty, reproductive lifespan, and menopausal periods given that these different periods of women's reproductive life are ordered in time with temporal relations. Analyses for age at menarche were further adjusted for childhood silhouette and father's and mother's socio-professional categories at adolescence (model 2A). Analyses for reproductive lifespan period were further adjusted for age at menarche, childhood silhouette, father's and mother's socio-professional categories at adolescence, silhouette at 18 years old, education, heavy physical labor, smoking status, and alcohol consumption (model 2B). Analyses for menopausal period (ie, from menopause onset) were further adjusted for age at menarche, nulliparity, breastfeeding, lifetime duration of breastfeeding, childhood silhouette, father's and mother's socio-professional category at adolescence, silhouette at 18 years old, education, heavy physical labor, smoking status, and alcohol consumption, body mass index, height, marital status, revenues, physical activity, rheumatological diseases, history of breast, uterine, and ovarian cancers, hypertension, hypercholesterolemia, diabetes, cardio- and cerebrovascular diseases, depressive symptoms, and MMSE as a marker of cognitive function (model 2C). For reproductive lifespan period and menopausal period characterized by different exposures variables, those that were significantly associated with GS in models 2B (reproductive lifespan period) and 2C (menopausal period) were simultaneously included in multiadjusted models adjusted for the same confounders (model 3B and model 3C, respectively).

For ordinal variables, linear tests of trends across categories of exposure were conducted using the median of each group. For categorical variables, global tests were used as well as homogeneity tests as appropriate.

Analyses were performed using SAS 9.4 (SAS Institute Inc.) and R software (x64 3.6.1; Multiple Imputation by Chained Equations package). To take into account multiple comparisons, we considered the different stages of hormonal exposure throughout life (ie, puberty, childbearing, menopause, contraceptive use, and hormone therapy use) and corrected the *P* value accordingly (.05/5). Results were then considered significant at the 1% alpha level.

Results

Figure 1 shows the flowchart of the study population selection. A total of 56 836 women aged ≥45 years were included in the CONSTANCES study between 2012 and 2020; hormonal characteristics were available for 54 678 women. Women who were pregnant, gave birth less than 6 weeks earlier, had Parkinson disease, and attended HSCs during periods without

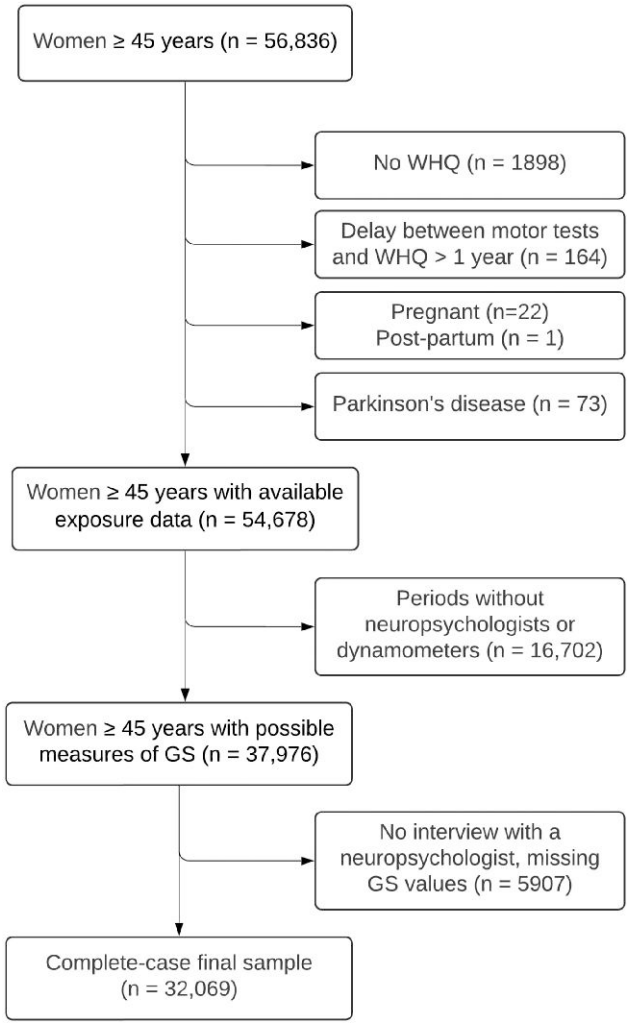

Figure 1. Flowchart of the population selection.

neuropsychologists or dynamometers were excluded, leaving 37 976 women for analysis. GS was missing for 5907 women (15.5%) who were significantly younger, more educated, less physically active, more often single, nulliparous or had fewer children, had a lower household income, and a worse health profile compared to women with available GS (see Supplementary Tables S1 and S2) [33].

After multiple imputation, mean GS was 26.6 kg (SE = 0.32). Women were aged 57.2 years on average (SE = 0.13). A 1-year increase in age was associated with a decrease in GS of 0.28 kg. As Table 1 indicates, lower GS were found in women who were small in stature ($P < .01$) and had comorbidities ($P < .01$). Higher GS was observed among women who had higher education level, higher monthly income ($P < .01$), who were physically active ($P < .01$), ever smoked ($P < .01$), and had a high MMSE ($P < .01$).

The mean age at menarche was 13.0 (SE = 0.03) years and 14% of women were nulliparous. Among parous women, the mean parity was 2.2 (SE = 0.02), and 29% of women had never breastfed. Almost 90% of the sample had ever used a contraceptive pill and most of them had used it for more than 5 years (71.7%). Seventy-four percent of women were postmenopausal, with a mean age at menopause of 49.9 (SE = 0.04) years and most experienced a natural menopause (86%). Sixty percent of postmenopausal women had never used HT, whereas approximately 14% were current users (Table 2). Association of GS with general characteristics, characteristics of reproductive history, and exogenous hormones on study population before imputation were markedly similar (Supplementary Tables S3 and S4) [33]. Associations between baseline characteristics and hormonal exposure are presented in Supplementary Tables S5 to S10 [33]. Associations between characteristics of puberty, reproductive lifespan, and menopausal periods with GS are summarized in Tables 3-5, respectively. Increasing age at menarche was significantly associated with GS (β_{M2A} per 1 year = 0.14; 95% CI, 0.10-0.17).

Nulliparity was negatively associated with GS (β_{M2B} = −0.23; 95% CI, −0.40 to −0.06) and there was a significant, positive linear association between parity and GS among parous women ($\beta_{M2B} \geq 3$ vs $1 = 0.35$; 95% CI, 0.18-0.52, *P-linear trend* <.01), whereas age at first birth was not associated with GS. Never having breastfed was associated with a lower GS ($\beta_{M2B} = -0.41$; 95% CI, −0.55 to −0.28) and among women who breastfed at some point in their life, GS increased with lifetime duration of breastfeeding (model 2B, *P-linear trend* <.01). There was no association between contraceptive pill use and GS but, among women who had ever used it, we found an inverse association of GS with duration of pill use (model 2B, *P-linear trend* <.01). In the multiadjusted model 3B, associations remained significant for lifetime duration of breastfeeding but were no longer significant for nulliparity, parity, and duration of pill use.

Compared to nonmenopausal women, postmenopausal women presented significant lower GS ($\beta_{M2C} = -0.74$; 95% CI, −0.93 to −0.54) and, among nonmenopausal women, the decrease in GS did not reach the significance for perimenopausal women compared to premenopausal ($\beta_{M2C} = -0.56$, 95% CI, −1.04 to −0.07). Type of and age at menopause, reproductive lifetime duration, and time since onset of menopause were not significantly associated with GS. Finally, relative to HT never use, the association between GS and HT past use was negative ($\beta_{M2C} = -0.25$; 95% CI, −0.42 to −0.07) but no significant association was observed with HT current use ($\beta_{M2C} = 0.24$; 95% CI, 0.01-0.46; *P-heterogeneity* <.01). In addition, among HT current users, age at current HT initiation was not significantly associated with GS. In multiadjusted model 3C, these associations remained unchanged.

Discussion

In this cross-sectional analysis, GS increased with age at menarche and lifetime duration of breastfeeding. In addition, nonmenopausal women had higher GS than postmenopausal women; however, type of and age at menopause did not play a role. Finally, HT past use was associated with lower GS.

To our knowledge, only 1 previous study investigated the relationship between age at menarche and physical performance later in life [27]; age at menarche was not associated with handgrip strength. However, some differences, including younger age of participants and reduced statistical power, could explain disparities between these previous data and the current findings. Another study compared GS in young female athletes before and after age at menarche [31] and found that postmenarche girls had higher GS than premenarche girls. However, this difference was explained primarily by age and height.

Table 1. General characteristics of the study population

Characteristics			**Tertiles of GS (kg)**		
***N* = 37 976**			**1st**	**2nd**	**3rd**
Maximal grip strength (kg), M (SE)		26.6 (0.32)	20.9 (0.07)	26.5 (0.07)	32.4 (0.07)
Age (y), M (SE)		57.2 (0.13)	59.1 (0.16)	57.4 (0.16)	54.9 (0.16)
Anthropometric characteristics					
Height (cm), M (SE) (MV = 301)		161.6 (0.18)	159.3 (0.20)	161.6 (0.20)	164.2 (0.20)
BMI (kg/m^2), M (SE) (MV = 793)		25.0 (0.14)	25.1 (0.14)	24.9 (0.14)	25.0 (0.14)
Childhood silhouette, % (MV = 13 822)	Slim	25.6	27.6	25.5	23.5
	Normal	51.7	49.4	52.0	53.8
	Overweight	22.7	23.0	22.5	22.7
Silhouette at 18 y, % (MV = 13 564)	Slim	31.1	32.9	31.2	29.1
	Normal	55.9	53.3	56.3	58.2
	Overweight	13.0	13.8	12.5	12.7
Socioeconomic characteristics, %					
Father's socio-professional category at adolescence (MV = 2303)	Farmer	11.4	10.9	11.6	11.6
	Craftsman/trader/business owner	14.7	15.3	15.2	13.8
	Manager/executive/upper intellectual	19.2	17.6	19.5	20.6
	Intermediate profession	15.2	14.0	15.2	16.4
	Employee	10.6	10.7	10.5	10.5
	Manual worker	26.8	29.4	26.0	24.9
	No occupation/other	2.1	2.1	2.0	2.2
Mother's socio-professional category at adolescence (MV = 1354)	Farmer	9.9	9.4	10.1	10.2
	Craftsman/trader/business owner	8.2	8.5	8.6	7.4
	Manager/executive/upper intellectual	3.9	3.4	3.8	4.5
	Intermediate profession	10.0	8.7	9.9	11.4
	Employee	17.3	16.2	16.8	18.8
	Manual worker	7.5	8.5	7.1	6.9
	No occupation/other	43.2	45.3	43.7	40.8
Marital status (MV = 923)	Couple	62.6	61.4	62.5	63.9
	Single	14.8	14.6	14.4	15.4
	Separated/divorced/widowed	22.5	24.0	23.1	20.6
Monthly income (MV = 3493)	<€1500	10.8	13.0	10.4	8.9
	€1500-€2800	28.7	31.5	28.5	26.1
	>€2800	60.5	55.5	61.1	65.0
Education (MV = 759)	No/primary education	29.9	35.6	29.6	24.3
	High school degree	17.2	17.3	17.0	17.3
	Bachelor/more/others	52.9	47.2	53.4	58.4
Heavy physical labor (MV = 2608)	Yes	28.2	29.2	28.0	27.4
Health behaviors, %					
Physical activity (MV = 1988)	Inactive	22.1	22.7	21.6	22.0
	Moderately active	44.3	43.7	44.2	45.0
	Very active	33.6	33.6	34.3	33.0
Alcohol (MV = 5595)	No consumption	19.5	21.5	19.3	17.6
	Moderate consumption	72.3	70.6	72.5	73.9
	Unsafe consumption	8.2	7.8	8.3	8.5
Smoking status (MV = 1834)	Ever	48.9	46.1	49.3	51.5
Medical conditions, %					
Hypercholesterolemia (MV = 109)		34.0	37.6	34.6	30.0
Hypertension (MV = 105)		31.9	34.7	31.8	29.2
Diabetes (MV = 99)		3.2	4.1	2.9	2.5
Depressive symptoms (MV = 3104)		27.7	30.7	26.7	25.5
MMSE score (MV = 5241)	≥29	53.8	50.2	54.0	57.4
	28	18.2	18.6	18.1	18.0
	<28	27.9	31.2	27.9	24.6
CVD (MV = 799)		1.8	2.1	1.7	1.5
Rheumatological diseases (MV = 1771)		17.0	21.9	15.7	13.2
History of uterine or ovarian cancer		0.5	0.6	0.5	0.4
History of breast cancer		4.6	5.7	4.4	3.7

(*continued*)

Table 1. Continued

Characteristics			Tertiles of GS (kg)		
***N* = 37 976**			**1st**	**2nd**	**3rd**
Test conditions, %					
Type of material	Hydraulic dynamometer	21.7	26.8	19.8	18.0
	Electronic dynamometer	78.3	73.2	80.2	82.0
Specific conditions for GS test		14.1	18.7	12.6	10.6

After adjustment for age, all characteristics at baseline were significantly associated with GS (*P* value <.01).
Abbreviations: BMI, body mass index; CVD, cardio- and cerebrovascular diseases; M, mean; MMSE, Mini-Mental State Examination; MV, missing values before multiple imputation.

Table 2. Characteristics of reproductive history and exogenous hormones use of the study population

Characteristics			Tertiles of GS (kg)		
***N* = 37 976**			**1st**	**2nd**	**3rd**
Characteristics of puberty period					
Age at menarche (y), M (SE) (MV = 1856)		13.0 (0.03)	12.9 (0.03)	13.0 (0.04)	13.1 (0.03)
Characteristics of reproductive lifespan period					
Nulliparous, % (MV = 583)	Yes	14.2	15.0	14.0	13.6
Parity[a], % (MV = 7)	1	19.4	20.9	19.9	17.7
	2	48.6	48.3	48.5	48.8
	≥3	32.0	30.8	31.4	33.5
Age at first birth[a] (y), M (SE) (MV = 121)		26.6 (0.27)	26.1 (0.28)	26.7 (0.28)	27.1 (0.28)
Breastfeeding[a], % (MV = 1304)	Never	29.1	32.6	29.1	25.5
Duration of breastfeeding[a,b] (mo), % (MV = 402)	1-5	30.7	33.9	30.4	28.0
	5-10	34.3	33.7	34.8	34.4
	≥10	35.0	32.4	34.8	37.6
Contraceptive pill use, % (MV = 2119)	Ever	89.9	88.1	90.5	91.3
Duration of contraceptive pill use[c] (y), % (MV = 485)	<1	6.1	6.9	5.8	5.6
	1-5	22.2	23.5	22.0	21.0
	≥5	71.7	69.6	72.2	73.4
Age at first contraceptive pill initiation[c] (y), M (SE) (MV = 1375)		20.7 (0.07)	21.3 (0.09)	20.7 (0.09)	20.2 (0.09)
Characteristics of menopausal period					
Menopausal status, % (MV = 908)	Premenopausal	24.3	15.5	22.8	34.6
	Perimenopausal	1.4	1.1	1.5	1.7
	Postmenopausal	74.3	83.4	75.7	63.7
Type of menopause[d], % (MV = 276)	Natural	86.3	86.6	86.8	85.3
	Surgical	10.6	10.2	10.4	11.4
	Iatrogenic	3.1	3.2	2.8	3.3
Age at menopause[d] (y), M (SE) (MV = 554)		49.9 (0.04)	50.0 (0.06)	50.0 (0.07)	49.7 (0.07)
Reproductive lifetime duration[d] (y), M (SE) (MV = 1863)		36.9 (0.03)	37.1 (0.05)	37.0 (0.06)	36.6 (0.06)
Time since onset of menopause[d] (y), M (SE) (MV = 607)		10.2 (0.11)	11.1 (0.12)	10.2 (0.12)	8.9 (0.12)
HT use[d], % (MV = 7610)	Never	59.8	56.8	60.1	63.7
	Past	26.3	30.1	26.5	21.1
	Current	13.8	13.1	13.4	15.3
Age at current HT initiation[d,e] (y), M (SE) (MV = 565)		50.9 (0.07)	50.9 (0.11)	51.0 (0.14)	50.8 (0.13)

Abbreviations: HT, hormone therapy; M, mean; MV, missing values before multiple imputation.
[a]Among parous women.
[b]Among women who ever breastfed.
[c]Among ever users of pill.
[d]Among postmenopausal women.
[e]Among current users of HT.

Few studies have examined the association between characteristics of parity history and GS [24, 25]. Our results are consistent with 2 studies showing no association of parity or maternal age at first birth with GS [24, 25]. Nevertheless, contrary to Harville et al, our data did not reveal a significant association between nulliparous status and lower GS in the most adjusted model [25]. To our knowledge, no previous study has examined the role of breastfeeding on physical

Table 3. Association between characteristics of reproductive history during the puberty period and grip strength (kg)

Exposure	Model 1		Model 2A	
	Beta (95% CI)	*P*	Beta (95% CI)	*P*
Age at menarche				
+1 y	0.13 (0.10-0.17)	<.01	0.14 (0.10-0.17)	<.01
≤12 y	Reference		Reference	
12-14 y	0.30 (0.15-0.44)	<.01	0.28 (0.13-0.42)	<.01
≥14 years	0.53 (0.39-0.66)	<.01	0.54 (0.40-0.68)	<.01
		<.01[a]		<.01[a]

Model 1: adjusted for center, age centered on 57.1 (mean), type of material, and specific conditions for grip strength test. Model 2A: model 1+ childhood silhouette, and father's and mother's socio-professional category at adolescence.
[a]*P* for linear trend.

performance. In our study, lifetime duration of breastfeeding was positively associated with GS, while adjusting for other characteristics of reproductive live and several confounders, including education level, which is strongly associated with both breastfeeding status and GS.

Several studies have examined the role of menopause-related exposures [12, 13, 16, 17, 30, 38] but none in a large French population. Our results are consistent with cross-sectional studies that reported lower GS during and after the menopausal transition [12, 13, 39]. Other studies showed that nonmenopausal women had higher GS than postmenopausal women [17, 38], although results were not statistically significant likely because of insufficient statistical power [17, 38]. Our findings are also consistent with longitudinal studies showing a significant decline in GS from early perimenopause to postmenopause [30] or from premenopause to natural postmenopause [16].

The association between age at and type of menopause with GS has been less frequently investigated [16, 17, 19, 40]. Consistently with previous data, we failed to identify an association for artificial menopause [16, 17] or for age at menopause [40]. By contrast, another study reported lower GS among women who experienced natural menopause before 40 years [19]; however, the previous study focused on women who experienced natural menopause.

To our knowledge, this study is the first to examine the role of contraceptive pill use in GS and did not find a significant association between duration of contraceptive pill use and GS. These results were nevertheless consistent with a recent systematic review that provided no evidence for a protection of combined hormonal contraceptive use against musculoskeletal pathophysiology and injury [41].

There is an extensive and controversial literature on the role of hormonal supplementation after menopause; 1 difficulty in interpreting these studies lies in different methodological approaches and types of HT. Although some studies indicate that HT current use could be associated with higher GS [22, 42], our results were consistent with others that demonstrated no association [17, 20, 43, 44]. Recently, Camara et al suggested a possible differential association of duration of HT use with sarcopenia by level of physical activity among women [45]. This could potentially explain, at least in part, heterogeneity in the literature regarding the impact of HT on physical performance. We also found that past HT users had lower GS. To our knowledge, no previous study has specifically investigated past HT use in relation with GS. It has been suggested that the benefit of HT on muscle mass, performance, and composition is limited in time [11, 21, 46]. However, we cannot exclude an indication bias if HT past users had more frequently disorders related to low ovarian hormone levels, such as joint pains that are potentially associated with impaired physical performance and motivating an exogenous supplementation prescription.

Physical performance results from complex interactions between the muscular, skeletal, nervous, and cardiovascular systems. GS is a simple isometric test of upper body muscle strength more likely affected by muscular function and bone integrity. Higher GS among women before menopause is consistent with the hypothesis of a protective effect of estradiol and progesterone on muscular atrophy. The perimenopausal period is characterized by irregular cycles and climacteric signs resulting from progressive qualitative and quantitative alterations in ovarian follicular reserves. Follicles become less able to respond to FSH and produce inhibin, resulting in increased FSH and endogenous hyperstimulation of the ovaries, leading to a predominantly hyperestrogenic syndrome. Ovulations decrease in quality and the resulting corpus luteum becomes unable to secrete sufficient progesterone, thereby contributing to shorter menstrual cycles. Alternating phases of ovarian hypo- and hyperactivity characterize the hormonal disorganization of perimenopause [47]. However, in late perimenopause, ovarian activity progressively decreases and, between 6 months before the last menstrual period and 1 year after, estradiol concentrations decrease by 60% [48], whereas postmenopausal HT users have higher estrogens levels than nonusers [49]. Biological aging is associated with muscle atrophy, which contributes to muscular weakness and sarcopenia [7, 50]. Estrogens receptors are expressed at multiple sites along the neuromuscular system [51], and growing evidence suggests that estrogens are involved in the maintenance of muscle mass [10, 52] and affect muscle recovery following injury [50, 53]. Nevertheless, loss of strength in aging women cannot be fully explained by loss of muscle mass because the specific force (force generation normalized to muscle size) also declines, suggesting an impairment in muscle contraction [50]. Moreover, dynapenia (ie, the age-associated loss of muscle strength independent of muscle atrophy) is accelerated by menopausal transition [21]. As evidence in support of this hypothesis, specific force and myosin function were found to be greater in muscle fibers from biopsies of monozygotic twins on HT users compared to nonusers [46].

Table 4. Association between characteristics of reproductive history and exogenous hormones use during reproductive lifespan period and grip strength (kg)

Exposure	Model 1		Model 2B		Model 3B	
	Beta (95% CI)	*P*	Beta (95% CI)	*P*	Beta (95% CI)	*P*
Nulliparous						
Yes vs no	−0.25 (−0.43 to −0.07)	<.01	−0.23 (−0.40 to −0.06)	.01	0.15 (−0.07 to 0.38)	.18
Parity[a]						
1	Reference		Reference		Reference	
2	0.33 (0.16-0.49)	<.01	0.23 (0.07-0.39)	<.01	0.14 (−0.03 to 0.30)	.10
≥3	0.48 (0.30-0.66)	<.01	0.35 (0.18-0.52)	<.01	0.15 (−0.04 to 0.33)	.12
		<.01[d]		<.01[d]		.15[d]
Age at first birth[a]						
+1 y	0.04 (0.03-0.05)	<.01	0.00 (−0.01 to 0.02)	.51		
<24 y	Reference		Reference			
24-28 y	0.50 (0.35-0.66)	<.01	0.09 (−0.07 to 0.24)	.28		
≥28 y	0.62 (0.46-0.78)	<.01	0.11 (−0.06 to 0.27)	.20		
		<.01[d]		.54[d]		
Breastfeeding[a]						
Never vs ever	−0.66 (−0.80 to −0.52)	<.01	−0.41 (−0.55 to −0.28)	<.01	−0.16 (−0.33 to 0.02)	.08
Lifetime duration of breastfeeding[a,b]						
1-5 mo	Reference		Reference		Reference	
5-10 mo	0.47 (0.28- 0.65)	<.01	0.34 (0.16-0.51)	<.01	0.31 (0.13-0.49)	<.01
≥10 mo	0.60 (0.41- 0.79)	<.01	0.45 (0.27-0.63)	<.01	0.39 (0.20-0.59)	<.01
		<.01[d]		<.01[d]		<.01[d]
Contraceptive pill use						
Never vs ever	−0.12 (−0.32 to 0.08)	.23	0.14 (−0.06 to 0.33)	.16	−0.02 (−0.33 to 0.29)	.90
Duration of contraceptive pill use[c]						
<1 y	Reference		Reference		Reference	
1-5 y	0.06 (−0.23 to 0.35)	.70	−0.09 (−0.37 to 0.18)	.50	−0.10 (−0.37 to 0.18)	.49
≥5 y	−0.02 (−0.30 to 0.26)	.89	−0.25 (−0.51 to 0.02)	.06	−0.23 (−0.49 to 0.03)	.08
		.50[d]		<.01[d]		.02[d]
Age at contraceptive pill initiation[c]						
+1 y	0.00 (−0.02 to 0.01)	.58	0.01 (0.00-0.03)	.10		
≤17	Reference		Reference			
17-21 y	0.03 (−0.14 to 0.19)	.75	0.00 (−0.16 to 0.16)	.98		
≥21 y	−0.01 (−0.21 to 0.19)	.94	0.13 (−0.06 to 0.32)	.18		
		.68[d]		.60[d]		

Model 1: adjusted for center, age centered on 57.1 (mean), type of material and specific conditions for grip strength test. Model 2B: model 1+ age at menarche centered on 12.9 (mean), childhood silhouette, father's and mother's socio-professional category at adolescence, silhouette at 18 years old, education, heavy physical labor, smoking status, and alcohol consumption. Model 3B: model 2B and mutually adjusted for significant hormonal exposures in model 2B.
For models 1 and 2B:
[a]Adjusted for nulliparous (yes/no).
[b]Adjusted for breastfeeding (never/ever).
[c]Adjusted for contraceptive pill use (never/ever).
[d]*P* for linear trend.

In addition to muscular function, maintenance of BMD and prevention of osteoporotic fractures are also potential biological mechanisms involved in GS maintenance [54]. BMD naturally declines with aging and ovarian hormones can have beneficial impact: estrogens are key regulators of bone metabolism and inhibit bone resorption [55, 56], whereas progesterone stimulates bone formation [57, 58]. Menopausal transition has a significant effect on bone loss in women at high risk of osteoporosis and fractures [52]. We therefore hypothesized that part of the beneficial effect of hormonal exposure on GS may be explained by positive effect of ovarian hormones on preservation of bone integrity. Regarding the long-term effects of breastfeeding on BMD, the literature is controversial [59, 60]. Our results could appear to be in contradiction with a protective effect of estrogens because longer duration of breastfeeding may be associated with lower estrogens exposure [61]. However, there is a consensus that pregnancies and longer cumulative duration of breastfeeding are associated with a reduced risk of fracture [62], a finding attributed to changes in bone structural properties during lactation, independently of changes in BMD.

Table 5. Association between characteristics of reproductive history and exogenous hormones use related to menopausal period and grip strength (kg)

Exposure	Model 1		Model 2C		Model 3C	
	Beta (95% CI)	*P*	Beta (95% CI)	*P*	Beta (95% CI)	*P*
Menopausal status						
Non-menopausal	Reference		Reference		Reference	
Postmenopausal	−0.87 (−1.07 to −0.67)	<.01	−0.74 (−0.93 to −0.54)	<.01	−0.78 (−0.98 to −0.58)	<.01
Type of menopause[a]						
Natural	Reference		Reference			
Artificial	0.03 (−0.16 to 0.22)	.76	0.12 (−0.07 to 0.31)	.23		
Iatrogenic	−0.10 (−0.49 to 0.29)	.61	0.10 (−0.34 to 0.53)	.66		
Surgical	0.07 (−0.15 to 0.29)	.53	0.12 (−0.09 to 0.33)	.25		
Oophorectomy[b]	0.03 (−0.34 to 0.41)	.86	0.13 (−0.22 to 0.49)	.47		
Hysterectomy	0.09 (−0.19 to 0.36)	.53	0.12 (−0.14 to 0.37)	.38		
		.59[d]/.40[e]		.40[d]/.65[e]		
		.74[d]/.67[f]		.53[d]/.68[f]		
Age at menopause[a]						
+5 y	0.06 (−0.01 to 0.13)	.10	−0.02 (−0.09 to 0.04)	.48		
Premature	−0.15 (−0.50 to 0.21)	.42	0.06 (−0.28 to 0.41)	.72		
Early	−0.13 (−0.35 to 0.10)	.26	0.04 (−0.17 to 0.25)	.69		
Normal	Reference		Reference			
Late	0.12 (−0.09 to 0.33)	.26	0.07 (−0.13 to 0.27)	.49		
		.07[g]		.96[g]		
HT use[a]						
Never	Reference		Reference		Reference	
Past	−0.30 (−0.49 to −0.12)	<.01	−0.25 (−0.42 to −0.07)	.01	−0.25 (−0.42 to −0.07)	.01
Current	0.25 (0.01-0.48)	.04	0.24 (0.01-0.46)	.04	0.24 (0.01-0.46)	.04
		<.01[d]		<.01[d]		< .01[d]
		<.01[b]		<.01[b]		<.01[b]
Age at current HT initiation[a,c]						
+1 y	0.01 (−0.04 to 0.05)	.74	−0.01 (−0.05 to 0.03)	.74		
≤49 y	Reference		Reference			
49-52 y	−0.34 (−0.85 to 0.17)	.19	−0.23 (−0.68 to0.23)	.33		
≥52 y	0.01 (−0.54 to 0.55)	.98	−0.17 (−0.68 to 0.34)	.51		
		.87[g]		.55[g]		
Reproductive lifetime duration[a]						
+5 y	−0.02 (−0.09 to 0.05)	.53	−0.03 (−0.09 to 0.04)	.46		
<36 y	Reference		Reference			
36-39 y	0.10 (−0.07 to 0.27)	.25	0.05 (−0.11 to 0.21)	.53		
>39 y	−0.02 (−0.19 to 0.15)	.79	0.00 (−0.17 to0.16)	.96		
		.90[g]		.98[g]		
Time since onset of menopause[a]						
+5 y	−0.07 (−0.14 to −0.01)	.03	0.02 (−0.04 to 0.08)	.51		
≤6.5 y	Reference		Reference			
6.5-13 y	−0.12 (−0.31 to 0.06)	.20	0.04 (−0.14 to 0.22)	.67		
≥13 y	−0.23 (−0.46 to −0.01)	.04	0.04 (−0.17 to 0.25)	.71		
		.04[g]		.73[g]		

Model 1: adjusted for center, age centered on 57.1 (mean), type of material, and specific conditions for grip strength test. Model 2C: model 1+ age at menarche centered on 12.9 (mean), nulliparity, breastfeeding, lifetime duration of breastfeeding, childhood silhouette, father's and mother's socio-professional category at adolescence, silhouette at 18 years old, education, heavy physical labor, smoking status and alcohol consumption, BMI centered on 24.9 (mean), height centered on 161.8 (means), marital status, revenues, physical activity, rheumatological diseases, history of breast cancer, history of uterine or ovarian cancer + hypercholesterolemia, hypertension, diabetes, cardio- and cerebrovascular diseases, depressive symptoms, and MMSE. Model 3C: model 2C and mutually adjusted for significant hormonal exposures in model 2C.
Abbreviations: BMI, body mass index; HT, hormone therapy; MMSE, Mini-Mental State Examination.
For models 1 and 2C:
[a]Adjusted for menopausal status (postmenopausal vs nonmenopausal).
[b]Bilateral oophorectomy.
[c]Adjusted for HT use (nonuse/current).
[d]*P* global test.
[e]Iatrogenic vs surgical.
[f]Bilateral oophorectomy vs hysterectomy.
[g]*P* for linear trend.
[h]Past vs current.

Our finding that increased age at menarche is associated with stronger GS could also contradict the initial hypothesis of a protective effect of estrogens because women with later age at menarche presented with shorter estradiol exposures [63]. However, osteoarthritis is less frequent among women with increased age at menarche compared to those experiencing menarche at younger ages [64]. Although we adjusted our models for rheumatological diseases, residual confounding could explain the positive association between increased age at menarche and GS.

Strengths of the present study include the large sample size, an objective measure of GS in middle-aged and elderly women, and detailed information on a wide range of hormonal exposures and confounders.

Our study also has limitations. First, the low participation rate (~8%) should lead to a caution regarding extrapolation of the results. Although some population groups may be underrepresented, the expected associations between GS and general characteristics were found. Moreover, previous empirical research has moderate consequences of the nonparticipation bias on association estimates [65], and we performed an adjustment for social and educational conditions, often correlated with participation in epidemiological studies [66]. Second, GS was not available for all participants. However, in an effort to circumvent this challenge, we used sophisticated multiple imputation to handle missing values and used auxiliary variables associated with physical performance in the imputation model to improve efficiency [36]. Third, because exposures were self-reported, we therefore cannot exclude recall bias and misclassifications. That being said, the proportions of the different characteristics of reproductive history are similar to those found in other studies of the French population [67] and this potential bias is likely to be nondifferential, leading to underestimation of associations. Fourth, we were unable to identify specific conditions that could affect hormonal exposure, such as polycystic ovary syndrome, which is estimated to affect approximately 10% of reproductive-aged women [68] or hypothyroidism, or specific treatments such as corticosteroids. Finally, dynamometers changed over the course of the study. However, all analyses were adjusted for the type of dynamometer and stratification showed no heterogeneity by type of material (data not shown).

In conclusion, specific characteristics of reproductive life and exogenous hormonal exposures could explain part of the GS heterogeneity in women aged 45 to 69 years. Although the negative association between menopausal transition and GS is consistent with our initial hypothesis of a beneficial effect of estradiol on physical performance, the positive association of GS with age at menarche and duration of breastfeeding, as well as the negative association with past HT use did not support our hypothesis. Future studies are warranted to clarify these findings and a broader hormonal construct needs to be explored, by approaching not exclusively estradiol but also longitudinal progesterone and testosterone exposure, to evaluate the influence of hormonal exposure on women's musculoskeletal function and the arthritic conditions. Finally, although our study is limited to markers of hormonal exposure, biological dosages of ovarian hormones could be of considerable interest to disentangle the complex endocrinological mechanism of ovarian hormones on physical performance, and should be considered for future epidemiological studies.

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The sponsors had no role in the design, analysis, or preparation of the paper. The authors declare that they have no conflict of interest.

Data Availability

No data are available. The data of the CONSTANCES cohort are protected by our national regulatory agency ("Commission nationale de l'informatique et des libertés"). However, the CONSTANCES cohort is an open epidemiological infrastructure and access to study protocols and data is available on justified request.

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