JOURNAL OF WOMEN'S HEALTH
Volume 24, Number 1, 2015

DOI: 10.1089/jwh.2014.4839

Reproductive History and Chronic Hepatic Steatosis in the Michigan Study of Women's Health Across the Nation

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Abstract

Background: Reproductive history, particularly maternal age at most recent birth, may reflect lower risk for chronic disease and mortality due to socioeconomic factors, lifestyle behaviors, or genetics. Reproductive history has not been examined with respect to hepatic steatosis, the most common liver disease in the United States. Our objective was to examine the association between reproductive history and hepatic steatosis.
Methods: We examined the association between reproductive history characteristics—specifically age at most recent birth—and the odds of moderate to severe hepatic steatosis using a population-based retrospective cohort study of women who underwent hepatic ultrasound at the Michigan site of the Study of Women's Health Across the Nation ($n = 331$).
Results: Women who gave birth at ≥35 years of age comprised 19% of the study population and were similar to other women regarding sociodemographic history and health behaviors. In multivariable analyses adjusting for age, race/ethnicity, chronic disease, and medications associated with hepatic steatosis, age at birth ≥35 years was associated with significantly decreased odds of hepatic steatosis (adjusted odds ratio [OR] 0.41, 95% confidence interval [CI] 0.20–0.87), which was attenuated after adjustment for waist circumference (OR 0.51, 95% CI 0.24–1.10). Other reproductive factors including gravidity, parity, miscarriages and abortions, recall of gestational weight gain, breastfeeding, age at first birth, and age at final menstrual period were not associated with hepatic steatosis.
Conclusions: Women who were older at their most recent birth had a reduced odds of hepatic steatosis, possibly associated with their lower waist circumference.

Introduction

Nonalcoholic hepatic steatosis, also known as fatty liver disease, is the most common liver disease in the United States[1] and may account for one-third of newly diagnosed chronic liver disease.[2] Hepatic steatosis is a precursor to liver inflammation and cirrhosis[3] and also may be a risk factor for diabetes, poorer glycemic control among adults with diabetes, impaired renal function, and cardiovascular events.[4] In one population-based report, hepatic steatosis affected one-quarter of non-Hispanic white and African American women who were approximately 45 years of age.[5] Risk factors include metabolic syndrome and associated conditions such as polycystic ovarian syndrome (PCOS)[6], menopause,[7] and sex hormone levels,[8] as well as specific polymorphisms such as patatin-like phospholipase domain-containing protein 3 (PNPLA3).[4] We have previously reported that hepatic steatosis affected postmenopausal non-Hispanic white women more often than African American women and was associated with greater waist circumference, an adverse lipid profile, and hypoglycemic medication use, as well as sex hormone binding globulin (SHBG).[9] Therefore, it is important to identify risk factors for hepatic steatosis, particularly those that occur before midlife.

One set of potential risk factors is reproductive history, including factors such as maternal age at birth, gravidity, and parity. Although these factors are straightforward to ascertain and occur prior to the peak prevalence of liver disease, they have not been examined with respect to future chronic liver disease. In particular, women's age at their most recent pregnancy might be particularly relevant for future chronic disease risk. Multiple studies have observed an association between

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older maternal age and exceptional longevity.[10–13] While the mechanisms are speculative, behavior and genetics predisposing to longer life may also prolong the reproductive period. The disposable soma theory states that there is a tradeoff in energy allocation between reproductive fitness and repair, so that women who maintain fertility are able to do so because they need to devote less energy to maintenance of other organ systems.[14,15] Perls and Fretts have hypothesized that longevity associated genetic variants predisposing to longevity could also facilitate a longer period of childbearing.[11]

Maternal age at most recent birth reflects women's ovarian health or ovarian ''reserve,''[16] as well as socioeconomic factors, cultural choices, and partner health. In one cohort study, primiparous mothers with a birth ≥ 35 years of age (i.e., ''advanced maternal age'') were more educated, more likely to be employed, and of higher socioeconomic status than women who were not of advanced maternal age.[17] Some, but not all, of these women had experienced fertility difficulties. [17] Thus, women who have a later age at childbirth may have delayed childbearing in order to optimize educational and professional opportunities. These socioeconomic advantages may translate into improved lifestyle behaviors, with lower risk for obesity and subsequent chronic disease,[18] and thus greater age at most recent birth can reflect these upstream socioeconomic factors. However, women who have a later age at childbirth may also have impaired fertility, which could translate into greater chronic disease risk. To our knowledge, the relationship between later-life pregnancy and chronic disease such as hepatic steatosis has not previously been examined.

The Study of Women's Health Across the Nation (SWAN) is an ongoing population-based cohort study designed to characterize biological and symptomatic changes that occur during and after menopause among women of different racial/ethnic backgrounds.[19] Data collected included a retrospective reproductive history including age at the most recent pregnancy. The Michigan SWAN site ascertained the presence of hepatic steatosis with ultrasound at the 2010 follow-up visit. Thus, we were able to assess the relationship between age at most recent birth from women's reproductive years with the presence of postmenopausal hepatic steatosis. We hypothesized that greater age at most recent birth would be associated with lower odds of hepatic steatosis, and this association would be reduced after adjustment for anthropometrics.

Materials and Methods

Study population

The Study of Women's Health Across the Nation (SWAN) is a community-based cohort study conducted at seven sites in the United States. The sample for the current report was drawn from the Michigan site of the SWAN cohort. Recruitment procedures and the study design used for SWAN have been described elsewhere.[19–21] Briefly, in 1996–1997, women aged 40–55 years were screened from defined sampling frames at seven clinical sites throughout the United States. Eligible women were invited to participate in a longitudinal study of the natural history of the menopausal transition. To be eligible, women had to be between 42 and 52 years of age, have an intact uterus and at least one ovary, report having had a menstrual period in the previous 3 months, not report estrogen therapy in the 3 months prior to recruitment, and not currently be pregnant or breast-feeding. The Michigan site recruited women who self-identified as African-American or white. The cohort participated in a baseline clinical examination and continues to participate in follow-up examinations. All participants gave informed consent, and all study procedures were approved by the University of Michigan institutional review board.

All women at the Michigan site were invited to undergo hepatic ultrasound at the time of their 2010 follow-up visit. At that visit, 345 (85%) of the 406 Michigan SWAN women who participated underwent hepatic ultrasound. Women who did and did not undergo ultrasounds were similar with respect to demographic characteristics, alcohol and medication use, and anthropometric characteristics. Of the women with hepatic ultrasound measures, 14 women reported a history of cirrhosis or chronic liver disease due to viral hepatitis or hemachromatosis, and were excluded, leaving a total analytic sample of 331 participants for this report.

Data collection

The SWAN protocol includes annual ascertainment about menstrual status, reproductive events, socioeconomic status, history of diabetes, liver disease, alcohol and medication use from questionnaires, anthropometrics, blood pressure assessments, and serum measures. Data from the 2010 annual visit was used for this analysis. Reproductive history was assessed at the baseline visit; women were asked about the number of pregnancies, live births, miscarriages and abortions, weight gain with each pregnancy, and length of breastfeeding with each delivery, as well as maternal age at each delivery. Distributions of each variable were examined and categorized as described in Table 1. Women were categorized as having given birth at 35 years of age or older or not, based on classifications of increased infertility risk.[16] Forty-six women reported not having had a live birth, including 30 nulligravidas, and were characterized as not having a birth at ≥ 35 years of age.

Age at cessation of menses was based on the age at the last menstrual period. Alcohol intake was categorized as less than 1 drink per day versus >1 drink per day; only 12 women had 2 or more drinks per day. Information regarding use of medications reported to influence hepatic steatosis (including metformin, thiazolidinediones, orlistat, or sibutramine) was obtained, as was exogenous estrogen therapy. As part of study enrollment, no women used exogenous sex hormone therapy at baseline, but at the time of ultrasound, 28 women used exogenous estrogen therapy and 7 used progesterone therapy. No women used sibutramine, and only one woman used Orlistat. Weight and height, measured by use of calibrated scales and a stadiometer, were used to calculate body mass index (BMI) (kg/m^2). Waist circumference was measured to the nearest 0.1 cm with a measuring tape placed horizontally around the participant at the narrowest part of the torso.

All abdominal ultrasounds were performed by a single ultrasound technician unaware of the clinical and laboratory results of the participants on a Sonoline Elegra Ultrasound Imaging System (Siemens Medical Systems Inc.) using a 3.5 MHz transducer, a phantom (411 LE 0.5, GAMMEX rmi Ltd.,) and were also read by a radiologist who was blinded to participant profile. Ultrasound studies were performed and

Table 1. Baseline Characteristics of Women by Maternal Age at Most Recent Birth, Given as Mean (Standard Deviation) or Percentage

	No birth at age ≥35 years N=*269*	*Age ≥35 years* N=*62*	p *value*
Age, years	45.8 (2.8)	45.1 (2.5)	0.09
Race/ethnicity			0.18
Non-Hispanic white	38%	47%	
African American	62%	53%	
Education level			0.51
Less than high school	7%	3%	
High school	23%	15%	
More than high school, but less than college	46%	53%	
College	13%	15%	
More than college	11%	14%	
Difficulty paying for basics (from year 12)			0.20
Very hard	12%	13%	
Somewhat hard	32%	44%	
Not very hard at all	56%	44%	
Behaviors and Medications			
Alcohol use			
<1 drink per day at year 12	64%	66%	0.78
≥1 drink per day at year 12	36%	34%	
Smoker, at year 12	17%	16%	0.80
Diabetes at baseline	8%	2%	0.10
Metformin and thiazolidinediones at year 12	16%	13%	0.50
Estrogen use, ever	39%	40%	0.89
Reproductive history			
Ever had difficulty getting pregnant	20%	39%	0.002
Age at first menses, years	12.1 (3.4)	12.5 (1.8)	0.18
Age at first birth, years	20.7 (4.0)	25.9 (7.0)	**<0.01**
Age at most recent birth, years	26.8 (4.3)	37.6 (2.3)	**<0.01**
Gravidity, mean	3.0 (2.1)	4.6 (2.5)	**<0.01**
Parity, mean	2.7 (1.2)	3.4 (1.9)	**<0.01**
Any breastfeeding	32%	66%	**<0.01**
Age at final menstrual period, years[a]	51.4 (4.6) (*n*=174)	51.8 (3.1) (*n*=37)	0.51
Anthropometric characteristics			
Body mass index category at baseline			0.04
<25 kg/m^2	22%	36%	
25–29.9 kg/m^2	27%	30%	
≥30 kg/m^2	51%	34%	
Body mass index category at year 12			0.14
<25 kg/m^2	12%	15%	
25–29.9 kg/m^2	22%	32%	
≥30 kg/m^2	66%	53%	
Change in body mass index from baseline to year 12	4.0 (10.5)	4.0 (4.8)	0.95
Waist circumference (cm) at baseline, cm	95.0 (16.5)	90.1 (14.7)	**0.03**
Waist circumference (cm) at year 12, cm	101.9 (17.6)	98.0 (15.9)	0.11
Hip circumference (cm) at baseline, cm	114.7 (15.9)	110.1 (13.0)	**0.02**
Hip circumference (cm) at year 12, cm	117.8 (17.5)	113.5 (15.9)	0.08
Cumulative weight gain with pregnancies, kg[b]	37.0 (21.9)	52.7 (37.7)	**0.003**
Quartile of weight gain with pregnancy,			<0.01
Quartile 1: <20.4 kg	35%	18%	
Quartile 2: 20.4–33.5 kg	23%	21%	
Quartile 3: 33.6–54.5 kg	24%	16%	
Quartile 4: >54.5 kg	17%	45%	

[a]In the Study of Women's Health Across the Nation, only calculated for women who underwent natural menopause.
[b]Excludes women without a pregnancy.

classified according to the protocol of the Edinburgh Type 2 Diabetes Study[22] and these procedures have been previously reported for the SWAN cohort.[9] For the purposes of this analysis, hepatic steatosis was characterized as moderate/severe or none.

Statistical analyses

First, we examined demographics, reproductive history, and body mass index and waist circumference by age at the most recent birth using *t*-tests for continuous variables and

Table 2. Metabolic Characteristics of Women Who Gave Birth at or After the Age of 35 Years Compared with Those Who Did Not

	No birth at ≥35 years	*≥35 years*		*No birth at ≥35 years*	*>35 years*	
	Non-Hispanic white women N=*101*	N=*29*	p *value*	*African-American women* N=*168*	N=*33*	p *value*
Waist circumference (cm)	102.3 (17.5)	97.7 (18.1)	0.21	101.6 (17.8)	98.3 (14.1)	0.31
Fasting glucose (mg/dL)	112.9 (66.5)	98.3 (29.2)	0.10	102.3 (38.0)	105.2 (45.9)	0.70
Fasting insulin (IU/L)[a]	18.1 (21.3)	11.8 (10.7)	0.06	18.5 (25.5)	15.0 (11.7)	0.82
Triglycerides (mg/dL)[a]	136.6 (32.5)	140.7 (64.1)	0.40	111.8 (56.5)	108.2 (43.5)	0.93
High-density lipoprotein (mg/dL)	57.3 (15.0)	57.9 (15.6)	0.86	55.5 (16.1)	56.7 (18.1)	0.71
Low-density lipoprotein (mg/dL)	118.0 (32.3)	138.3 (40.9)	<0.01	113.6 (35.3)	117.5 (36.5)	0.57
Systolic blood pressure (mmHg)	123.4 (16.0)	125.6 (23.1)	0.62	133.7 (19.4)	133.1 (20.0)	0.86
Diastolic blood pressure (mmHg)	70.3 (9.0)	71.7 (9.6)	0.48	75.0 (10.8)	78.0 (10.7)	0.15
Sex hormone binding globulin (nM/L)	56.7 (30.3)	56.4 (28.3)	0.96	55.1 (32.1)	57.6 (31.8)	0.69

[a]Wilcoxon rank-sum tests used.

chi-squared tests for categorical variables; Wilcoxon tests were used for comparison of variables with skewed distributions (Table 1). In a previous report, we noted that risk factors for hepatic steatosis in optimally fitting models included waist circumference, high-density lipoprotein cholesterol levels, SHBG levels, alcohol use, medication use, and race/ethnicity.[9] Waist circumference and markers of visceral adiposity, rather than BMI, was more strongly correlated with hepatic steatosis in that report as well as in other studies.[23–25] For the present report, we also compared the metabolic characteristics of women who had and had not given birth at or after 35 years of age by race/ethnicity (Table 2).

Next, we created multivariable logistic regression models that examined the association between age at most recent birth (continuous and using the cutpoint of 35 years) and hepatic steatosis, before and after adjustment for covariates associated with steatosis in bivariate analyses (i.e., age, race/ethnicity, alcohol use, and use of medications previously reported to influence hepatic steatosis) (Table 3).[9] As other metabolic variables were not associated with both age at most recent birth and hepatic steatosis in the prior report, these were not included in the models. To determine whether associations between reproductive history variables and hepatic steatosis were mediated or confounded by adiposity, we created models that further adjusted for waist circumference at baseline. We also created models that included an interaction term between race/ethnicity and reproductive history variables as well as models that stratified by race/ethnicity, as previous reports have noted racial/ethnic differences in hepatic steatosis;[9] however, interaction terms were not significant and a similar pattern of effects was noted within race/ethnicity. All analyses were conducted using SAS version 9.3 (SAS Institute).

Results

Table 1 shows the characteristics among women by whether or not they gave birth at ≥35 years of age. Women who gave birth at ≥35 years of age comprised 19% of the study population. These women were similar to women who did not give birth after 35 years of age regarding their age at enrollment, education level, and difficulty paying for basics, patterns of alcohol use, cigarette smoking, diabetes, and hypoglycemic medication use. Metformin was used in women with diagnosed diabetes. Women who gave birth at the age ≥35 years were older at the age of first birth as well as recent birth but were pregnant more often, had a greater number of deliveries, and were more likely to breastfeed than parous women who were younger at most recent birth. Women who gave birth at the age ≥35 years were more likely to report difficulty conceiving than women who had not given birth at advanced maternal age. Women had a similar age of menopause regardless of age at last birth. Over the approximately 12-year period, both women who gave birth at or after the age of 35 years and women who did not gained a significant amount of weight, as represented in their increase in

Table 3. Unadjusted and Adjusted Odds Ratios of Hepatic Steatosis by Maternal Age at Most Recent Birth

	Unadjusted OR [95% CI]	*Adjusted OR*[a] *[95% CI]*	*Adjusted OR*[b] *[95% CI]*
Age at most recent birth (continuous, years)	0.95 [0.91–0.998]	0.95 [0.91–0.998]	0.95 [0.91–1.001]
Age at most recent birth ≥35 years (reference is age at most recent birth <35 years)	0.42 [0.20–0.87]	0.41 [0.20–0.87]	0.51 [0.24–1.10]

[a]Adjusts for age, race/ethnicity, alcohol use (<1 drink per day vs. ≥1 drink per day), and use of medications for diabetes.
[b]Adjusts for factors above and waist circumference at baseline.
CI, confidence interval; OR, odds ratio.

BMI ($p<0.001$ from baseline), although this gain did not differ by recency of last birth (Table 1). Finally, anthropometric characteristics were similar between the two groups of women except that women who gave birth at ≥35 years had a BMI that was slightly lower at baseline and a significantly lower waist and hip circumference at baseline; anthropometric characteristics at the year of ultrasound did not differ significantly. Women who gave birth at age ≥35 years had greater cumulative weight gain with pregnancy.

In analyses stratified by race/ethnicity, women who had given birth at or after 35 years of age had a similar metabolic profile compared to women who had not (Table 2), except among non-Hispanic white women, low-density lipoprotein cholesterol was higher among women who had given birth more recently compared with women who had not. Fasting glucose and insulin levels were slightly, but not significantly, lower among women who had given birth at or after 35 years among white women.

Table 3 shows the odds of steatosis associated with characteristics of reproductive history. In unadjusted analyses, greater age at most recent birth was associated with a lower odds of hepatic steatosis when age was examined as a continuous variable as well as ≥35 years or <35 years. After adjustment for other risk factors for hepatic steatosis, the association persisted. After further adjustment for baseline waist circumference, the association was attenuated and of borderline statistical significance.

We conducted a series of sensitivity analyses to determine if the relationships between age ≥35 years at the most recent birth and steatosis were altered by socioeconomic variables or other aspects of the reproductive history. In bivariate comparisons, education level, difficulty for paying for basics, gravidity (continuously measured), parity (continuously measured), nulligravidity (yes/no), nulliparity (yes/no), and grand multiparity (>5 births) were not associated with hepatic steatosis. Breastfeeding was not associated with hepatic steatosis when categorized as none versus any ($p=0.18$) or as none, some, or any breastfeeding ($p=0.39$). Cumulative weight gain with pregnancies and quartile of pregnancy weight gain were also not associated with hepatic steatosis in bivariate comparisons ($p>0.20$ for both associations). In multivariable models including age at most recent pregnancy, additional adjustment for education, difficulty paying for basic needs, breastfeeding, cumulative weight gain during pregnancy, or BMI did not significantly alter the observed relationship. The association between age at most recent birth and steatosis was attenuated after the adjustment for age at the final menstrual period, although a significant number of women dropped out of the model due to the calculation of age at final menstrual period only for women who underwent natural menopause.

Discussion

We found that in a community-based, biracial cohort, women's reproductive history—specifically age at most recent birth—was associated with a lower odds of hepatic steatosis. This association was attenuated with adjustment for premenopausal waist circumference. To our knowledge, our findings are novel: other studies have not examined associations between reproductive history in general or age at most recent birth specifically and hepatic steatosis.

Greater age at most recent birth could have been associated with lower odds of hepatic steatosis for several reasons. Women with later births may be more socioeconomically advantaged with subsequently improved lifestyle behaviors and chronic disease risk. Although we observed that the relationship between age at most recent birth and steatosis persisted after adjustment for education and difficulty paying for basics, these measures may not have captured all aspects of socioeconomic status, including partner status.

Second, age at most recent birth is a potential marker for greater ovarian reserve, which can be clinically expressed as greater fecundity in reproductive-aged women or later age at menopause in older women. This greater reserve may have had favorable effects upon future hepatic steatosis. However, women who had a greater age at most recent birth actually reported greater difficulty with conception, suggesting that women with advanced maternal age at most recent birth did not necessarily have greater reserve.

Third, age at most recent birth was associated with decreased waist circumference. Adjustment for waist circumference attenuated the association between age at most recent birth and hepatic steatosis, suggesting that adiposity played a key role. Adiposity may reflect upstream factors, such as socioeconomic status translating to healthier lifestyle behaviors. Adiposity may also reflect ovarian health. In women, obesity may suppress ovulation and interfere with conception and implantation either due to PCOS[26] or irregular bleeding associated with excess body mass.[27] Similarly, in the Danish National Birth Cohort, there was a dose-response relationship between increasing BMI group and subfecundity, expressed as a time to pregnancy of greater than 12 months.[28] In rats, caloric restriction may suppress transition from primordial to developing follicles,[29] and, if extrapolated to humans, women with lower body weights may also have preservation of reserve.

Adjustment for age at final menstrual period attenuated the association between hepatic steatosis and age at most recent birth. However, age at the final menstrual period was similar in women who gave birth and who did not give birth at ≥35 years. Age at most recent birth may have had significant associations with steatosis while age at the final menstrual period did not, because women who underwent surgical menopause or were using hormones do not have a final menstrual period, and we may have been underpowered to assess a significant association.

We did not find relationships between other aspects of reproductive history and hepatic steatosis. Pregnancy is a risk factor for increased weight gain and abdominal girth,[30,31] although how much weight is retained varies widely between women.[32] Previous studies suggest that weight gained in pregnancy and retained after pregnancy includes fat as opposed to lean mass.[33–36] We did not find a direct association between cumulative pregnancy weight gain and hepatic steatosis, or number of pregnancies and hepatic steatosis, because pregnancy may not lead to significant accumulations of fat in the liver, even as it leads to increased fat mass and visceral fat deposition. Alternatively, it is possible that the associations between pregnancy and increases in hepatic steatosis during the reproductive years are attenuated as women age; in Michigan SWAN, hepatic steatosis was ascertained approximately 8 years after the menopausal transition. We also did not find relationships between breastfeeding and

hepatic steatosis, again, perhaps due to the time frame that we ascertained hepatic steatosis, or perhaps because breastfeeding does not affect hepatic fat deposition.

The strengths of this study include its population-based nature and longitudinal assessments of women from the perimenopause up to a decade into postmenopause. An additional strength is its use of women's reproductive history as an indicator of future chronic disease risk, and in particular, examination of maternal age at most recent birth and chronic liver disease. Limitations include the retrospective nature of the reproductive history data. While women most likely recall accurately their age at their most recent birth and number of pregnancies and deliveries, recall of cumulative weight gain weight gain with pregnancy may be subject to biases in recall. Retrospective assessment may have led to attenuation between cumulative pregnancy weight gain and hepatic steatosis. Another limitation is that while we speculate that age at last pregnancy may reflect ovarian reserve, we lack more precise markers that would lend insight into the mechanisms that could affect the deposition of liver fat. Such biologic markers, particularly anti-Müllerian hormone, have recently been reported in population-based studies and offer a promising tool for prediction of age at menopause as well as for chronic disease.[37]

Additional measures of liver function such as transaminases and viral titers were not obtained. Such information would determine whether the hepatic steatosis on ultrasound was also associated with inflammation, i.e. steatohepatitis, and the etiology. PCOS has been associated with both subfertility and metabolic syndrome,[38] a correlate of hepatic steatosis. Although women with PCOS were less likely to be included in the SWAN cohort due to the study inclusion criteria, it is possible that age at most recent birth and hepatic steatosis are associated by their relationship to PCOS.

Conclusions

In conclusion, we found that women's reproductive history, and particularly age at most recent birth, was associated with decreased odds of hepatic steatosis. Prospective studies are needed to reproduce these observations and to explore the associations between other markers of ovarian reserve, including biochemical markers, and hepatic steatosis. The role of reproductive history in other racial/ethnic groups at high risk of hepatic stenosis should be examined. As maternal age increases and the prevalence of chronic liver disease increases, it is important to understand whether the relationship between these reflects other risk factors or causality.

Acknowledgments

The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants U01NR004061, U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, and U01AG012495). The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH, or the NIH.

Clinical centers. University of Michigan, Ann Arbor: Siobán Harlow, PI 2011–present, MaryFran Sowers, PI 1994–2011; Massachusetts General Hospital, Boston, MA: Joel Finkelstein, PI 1999–present, Robert Neer, PI 1994–1999; Rush University, Rush University Medical Center, Chicago, IL: Howard Kravitz, PI 2009–present, Lynda Powell, PI 1994–2009; University of California, Davis/Kaiser: Ellen Gold, PI; University of California, Los Angeles: Gail Greendale, PI; Albert Einstein College of Medicine, Bronx, NY: Carol Derby, PI 2011–present, Rachel Wildman, PI 2010–2011, Nanette Santoro, PI 2004–2010; University of Medicine and Dentistry, New Jersey Medical School, Newark, NJ: Gerson Weiss, PI 1994–2004; and the University of Pittsburgh, Pittsburgh, PA: Karen Matthews, PI.

NIH Program Office. National Institute on Aging, Bethesda, MD – Winifred Rossi 2012 - present; Sherry Sherman 1994–2012; Marcia Ory 1994–2001; National Institute of Nursing Research, Bethesda, MD.

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Steering committee. Susan Johnson, current chair; Chris Gallagher, former chair.

We also thank the study staff at each site and all the women who participated in SWAN.

Author Disclosure Statement

No competing financial interests exist.

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