Contributions of the Nurses' Health Studies to Reproductive Health Research

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Objectives. To review the Nurses' Health Study's (NHS's) contribution to identifying risk factors and long-term health consequences of reproductive events.

Methods. We performed a narrative review of the NHS I, NHS II, NHS3, and Growing Up Today Study (GUTS) publications between 1976 and 2016.

Results. Collection of detailed reproductive history to identify breast cancer risk factors allowed the NHS to document an association between menstrual irregularities, a proxy for polycystic ovary syndrome (PCOS), and increased risk of diabetes and cardiovascular disease. The NHS II found that infertility associated with ovulation problems and gestational diabetes are largely preventable through diet and lifestyle modification. It also identified developmental and nutritional risk factors for pregnancy loss, endometriosis, and uterine leiomyomata. As women in NHS II age, it has become possible to address questions regarding long-term health consequences of pregnancy complications and benign gynecologic conditions on chronic disease risk. Furthermore, the NHS3 and GUTS are allowing new lines of research into human fertility, PCOS, and transgenerational effects of environmental exposures.

Conclusions. The multigenerational resources of the NHSs and GUTS, including linkages of related individuals across cohorts, can improve women's health from preconception through late adulthood and onto the next generation. (*Am J Public Health.* 2016;106:1669–1676. doi:10.2105/AJPH.2016.303350)

Some of the crucial design elements necessary to address the primary hypotheses of the Nurses' Health Study (NHS I) and the Nurses' Health Study II (NHS II) regarding the etiology of breast cancer have also made it possible to evaluate hypotheses regarding risk factors for benign gynecologic and obstetric pathology, as well as the implications of reproductive history for chronic diseases other than cancer. Because some of the key potential confounders and risk factors for breast cancer are reproductive life events, the collection of detailed information on reproductive history was embedded within the fabric of the NHS I and NHS II from the outset. Furthermore, because collection of data on reproductive life events such as pregnancies (including pregnancies not ending in a live birth), difficulties becoming pregnant, and use of hormonal and other forms of contraception have been prospective and regularly updated, it has been possible for investigators to use these as primary outcomes and exposures in pursuing new avenues of research within these cohorts.

Likewise, the systematic and periodic collection of key lifestyle characteristics such as diet and physical activity has also allowed the study of these as risk factors for reproductive events. These and other key design features of the NHS that have facilitated reproductive epidemiology research are summarized in Table 1. Over the years, reproductive health research has become a key area of investigation, allowing NHS scientists to make important contributions to areas as varied as androgen excess disorders, fertility and pregnancy loss, common pregnancy complications, endometriosis, uterine fibroids, and the evaluation of long-term health consequences—to offspring and women themselves—of reproductive events. An overview of the existing resources within the NHS cohorts to address hypotheses regarding reproductive events is summarized in the box on page 1671 and the most important contributions to date are summarized in Table 2. A complete list of NHS publications on the topics covered in this review can be found in the appendix, available as a supplement to the online version of this article at http://www.ajph.org.

MENSTRUAL CYCLE IRREGULARITIES RESEARCH

The earliest contribution of NHS I to improving our understanding of benign gynecologic conditions was in the form of a secondary outcome within an article focused on breast cancer risk.[27] Specifically, one of the earliest NHS articles reporting on the association between relative body weight and premenopausal breast cancer risk also reported a J-shaped association between body mass index (BMI) and the prevalence of irregular menstrual cycles,

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This article was accepted June 21, 2016.

doi: 10.2105/AJPH.2016.303350

TABLE 1—Design Features That Have Facilitated Reproductive Epidemiological Research in the Nurses' Health Studies

Design Feature	Methodological Advantages and Research Facilitated
Health professionals as study participants	High validity of self-reported outcomes, in some cases superior to women in the general population High commitment to contributing to health research without compensation and for extended periods of time
Repeated assessment of pregnancy and unsuccessful attempts to become pregnant	Allows the estimation of incidence rates of infertility Allows the identification of infertility cases among women who did not seek medical attention for evaluation or treatment of this condition Allows the prospective identification of lifestyle risk factors for infertility
Repeated assessment of pregnancy outcome and common complications	Allows the estimation of incidence and recurrence rates of multiple pregnancy complications Allows the use of the "pregnancies at risk" approach for studies of pregnancy complications Allows the identification of risk factors for incident pregnancy complications and other adverse pregnancy outcomes
Repeated assessment of benign gynecologic conditions	Allows estimation of incidence rates for gynecologic conditions on the basis of prospective data from women in the general population For endometriosis, NHS II estimates were the first incidence estimates based on this type of data
Long-term prospective follow-up from reproductive years through postmenopause	Allows the evaluation of risk factors for multiple reproductive disorders with different distributions of peak age of incidence ranging from conditions with highest incidence during early reproductive years to conditions peaking in incidence around and after menopause Allows the evaluation of reproductive events as risk factors for chronic noncommunicable diseases
Repeated assessment of diet and lifestyle	Allows novel research linking diet and lifestyle factors with infertility and gestational diabetes to an unprecedented extent and based on prospective data Makes available preconception diet and lifestyle data thus avoiding major methodological problems in epidemiological research of risk factors for pregnancy loss
Wide geographical distribution	Facilitates generalizability to geographically diverse populations Can take into account known regional patterns in exposures of interest (e.g., diet, obesity) and reproductive events (e.g., age at first birth, cesarean delivery rates) Makes possible the evaluation of geographically determined exposures, such as air pollution and the built environment, as risk factors for adverse reproductive outcomes
Multigenerational component	Allows the evaluation of hypotheses regarding developmental and transgenerational determinants of health and disease including up to 3 generations in a subset of the study (Mothers of NHS II participants, NHS II participants, and GUTS—offspring of NHS II participants) Facilitates using generational changes in confounding structure as an advantage to etiological research (e.g., changes in the association between smoking during pregnancy and socioeconomic factors over 2 generations to evaluate the long-term health impacts on offspring of maternal smoking)

Note. GUTS = Growing Up Today Study; NHS = Nurses' Health Study.

whereby women with the lowest and the highest BMI had a higher prevalence of irregular menstrual cycles.[27] Although the association of underweight and menstrual irregularities had been thoroughly studied by then and the relation between obesity and menstrual irregularities had been recognized since antiquity and redescribed in the 1930s, this study was the largest one to examine this association and to address the entire spectrum of BMI rather than focusing on underweight or overweight women alone.

This initial work opened the door to further reproductive research as NHS investigators realized that menstrual irregularities could be used as a proxy for polycystic ovary syndrome (PCOS) in large epidemiological studies. At that point, small clinical studies had identified an association between PCOS and metabolic abnormalities[28] but prospective data with definitive endpoints were scarce. The NHS was among the first prospective cohorts to identify that women with irregular menstrual cycles, one of the clinical manifestations of PCOS, were at increased risk for type 2 diabetes and heart disease.[1,2] Specifically, women with irregular menstrual cycles were found to have a 53% higher incidence of heart disease[2] and twice the incidence of type 2 diabetes[1] compared with women with regular menstrual cycles.

EXPANSION OF REPRODUCTIVE RESEARCH

The NHS II further expanded the possibilities of reproductive research. Participants in this second cohort were younger at baseline and tens of thousands of them became pregnant or tried to become pregnant within the first 10 years of the study. This allowed NHS investigators to conduct research aimed

OVERVIEW OF EXPOSURES AND REPRODUCTIVE OUTCOMES IN THE NURSES' HEALTH STUDIES

Exposures	Reproductive Life Events	Long-Term Health Outcomes
Air pollution	Menstrual cycle characteristics	Hypertension
Body weight	PCOS	Type 2 diabetes
Body weight at age 18 y	Infertility	Coronary heart disease
Physical activity	Fertility treatments	Stroke
Sedentary activity	Miscarriage or stillbirth	Breast cancer
Diet	Gestational diabetes	Ovarian cancer
Occupational factors	Preeclampsia	Systemic lupus erythematosus
Age at menarche	Breastfeeding	Rheumatoid arthritis
Oral contraceptive use	Preterm delivery	
Abuse	Low-birth-weight delivery	
Stress	Cesarean delivery	
Birth weight	Endometriosis	
Parental smoking	Fibroids	
DES exposure in utero		

Note. DES = diethylstilbestrol; PCOS = polycystic ovary syndrome.

at identifying risk factors for infertility, pregnancy loss, pregnancy complications, and benign gynecologic pathology.

Infertility

Up through the early 1990s, the most common design of epidemiological studies aimed at identifying risk factors for infertility was hospital-based case–control studies. This design presents at least 2 important methodological challenges. First, most couples who have difficulties getting pregnant never seek medical consultation for infertility resulting in possible selection bias for hospital-based studies. Second, there is the possibility of differential recall between cases and controls, which is particularly problematic for studying lifestyle factors, such as diet, in relation to infertility. The NHS II allowed investigators to identify risk factors for infertility in a prospective cohort, without need of recall of lifestyle factors and allowing inclusion of women who did not seek evaluation or treatment of infertility.

The earliest work that used data from NHS II identified a J-shaped association between adult BMI and anovulatory infertility as well as a relation between greater time spent in vigorous physical activities and lower risk of anovulatory infertility.[29] This article also highlighted how, among American women, overweight and sedentary behavior had a greater population impact on anovulatory infertility than underweight and overexertion, challenging the leading opinion at the time. This article motivated subsequent work aimed at identifying whether dietary and lifestyle factors known to influence insulin sensitivity, a key metabolic derangement in PCOS, would also be related to risk of infertility attributable to anovulation.

Intakes of trans fats, low-fat dairy foods, animal protein, soft drinks, and a higher dietary glycemic load were associated with a higher risk of anovulatory infertility whereas higher intakes of folic acid, nonheme iron, high-fat dairy, and vegetable protein were associated with a lower risk of this condition. The combination of these dietary factors into a single dietary pattern was related to a 66% lower risk of anovulatory infertility (top vs bottom quintile comparison) as well as a 28% lower risk of all other causes of infertility.[30] Furthermore, the combination of diet, weight control, and physical activity was found to explain nearly two thirds of the incidence of anovulatory infertility in this cohort[30] suggesting that the majority of cases of infertility caused by anovulation may be preventable through diet and lifestyle interventions. Overlapping dietary patterns have been related to lower risk of infertility in other cohorts by independent investigators.[3] More recently, NHS investigators have focused their efforts on environmental risk factors documenting a modest but significant increase in the risk of infertility with increasing residential proximity to major roads and increased exposure to particulate matter.[31]

Pregnancy Loss

Work in the identification of risk factors for pregnancy loss started with the evaluation of occupational risk factors. Among women participating in a substudy of occupational factors among nurses, it was shown that the risk of spontaneous abortion was elevated among women who were exposed to antineoplastic drugs (odds ratio [OR] = 1.94), sterilizing agents (OR = 1.39), and x-ray radiation (OR = 1.22) during the first trimester of pregnancy.[32] Work schedule characteristics such as night work and long work hours were also identified as risk factors for spontaneous abortion in this cohort.[33] Specifically, compared with women who worked "days only" shifts, women who worked "nights only" during the first

TABLE 2—Major Contributions of the Nurses' Health Studies to Reproductive Health Research

Area	Main Finding	References
Menstrual cycle irregularities	Women with irregular menstrual cycles are at increased risk for type 2 diabetes mellitus (2-fold) and CVD (53% increase).	1, 2
Fertility	Infertility associated with ovulation disorders is largely preventable. Nearly half of the cases (46%) could be attributed to poor diet alone, and the majority of cases (66%) could be attributed to poor diet, inactivity, and overweight.	3, online appendix
Fertility	Occupational exposures specific to nursing are related to decreased fecundity.	Online appendix
Adverse pregnancy outcomes	Prepregnancy weight loss (particularly among overweight women) and supplemental folic acid intake above the recommended intake for prevention of neural tube defects is related to lower risk of spontaneous abortion and stillbirth.	4, 5
Adverse pregnancy outcomes	GDM is largely preventable. Nearly half of all cases of GDM (48%) could be attributed to poor diet, inactivity, overweight, and smoking.	6, online appendix
Endometriosis	Incidence of endometriosis documented at earlier ages than previously reported and across demographic characteristics. This is the first study to evaluate risk factors for endometriosis specific to diagnostic phenotypes.	7
Endometriosis	This is the first prospective cohort study able to study risk factors for this condition, and the first study to identify a relation between in utero exposures as well as growth trajectories across the life course and endometriosis risk.	8–10
Endometriosis	This is the first study to identify modifiable risk factors including diet, lactation, physical activity, air pollution exposure, and rotating shiftwork.	11, online appendix
Uterine leiomyomata	This is the first study to prospectively document the direct relation between age and incidence among premenopausal women and the 3-fold increase for Black women compared with White women.	12
Uterine leiomyomata	This study demonstrated critical life course relationships between risk and reproductive milestones including age at menarche, age at first exposure to oral contraceptives, and age at first and last birth.	13, online appendix
Uterine leiomyomata	This is the first prospective study to confirm linear relation between blood pressure and risk of uterine leiomyomata, regardless of antihypertensive therapy, and with history of stress related to abuse or other acute or chronic exposures.	14, online appendix
Reproductive events and chronic disease	The association between birth weight and risk of CVD cannot be explained by socioeconomic conditions, smoking, diet, family history, and other risk factors for CVD.	15
Reproductive events and chronic disease	Women who experience pregnancies complicated by GDM or who deliver preterm are at increased risk for type 2 diabetes and hypertension later in life.	16–18
Reproductive events and chronic disease	A healthy diet, weight control, and increased physical activity can decrease the risk of type 2 diabetes among women with a history of GDM.	19–22
Reproductive events and chronic disease	Women with endometriosis are at increased risk for CVD, systemic lupus erythematosus, and rheumatoid arthritis.	23, 24
Reproductive events and chronic disease	Undergoing infertility treatment is not related to later risk of hypertension in the woman or to risk of autism spectrum disorders in the offspring.	25, 26

Note. CVD = cardiovascular disease; GDM = gestational diabetes mellitus. Appendix available as a supplement to the online version of this article at http://www.ajph.org.

trimester had a 60% increased risk of spontaneous abortion and women working more than 40 hours per week during the first trimester had a 50% increased risk of spontaneous abortion compared with women working 21 to 40 hours, even after adjustment for work schedule.[33]

More recently, attention has shifted to nutritional and lifestyle factors. With data from more than 25 000 pregnancies, NHS II investigators found that the risk of pregnancy loss was elevated in women who were overweight (RR = 1.07), class I obese (RR = 1.10), or class II and III obese (RR = 1.27) before pregnancy compared with normal-weight women.[4] Moreover, losing 4 kilograms or more since age 18 years was associated with lower risk of pregnancy loss (RR = 0.80), particularly among women who were overweight or obese in adolescence.[4] This latter result directly highlighted

the vast potential that weight modification before pregnancy could have on the prevention of spontaneous abortion.

The availability of prospectively collected preconception data on diet and lifestyle factors represents an enormous methodological advantage to advancing this field because it not only avoids some of the problems already highlighted for infertility research, but it also avoids one of the most pervasive methodological difficulties in pregnancy loss research. Specifically, the prospective data collection helps to differentiate lifestyle risk factors predating pregnancy loss from lifestyle factors that changed in response to early pregnancy—particularly nausea, a strong predictor of lower risk of pregnancy loss. As a consequence, contributions regarding dietary factors have been particularly important.

We have found that higher intake of folate from supplements was associated with reduced risk of spontaneous abortion and stillbirth.[5] Specifically, the adjusted risk difference of pregnancy loss in women who consumed 0 micrograms per day of folic acid compared with more than 730 micrograms per day was 3.1%.[5] Moreover, it was estimated that only 42 women would need to go from between 400 and 729 micrograms per day of supplemental folate (the current recommendation) to 730 or more micrograms per day of supplemental folate to prevent 1 spontaneous abortion from occurring. This study was also the first to find a protective association between folate intake and risk of stillbirth. In a subsequent analysis, it was shown that 3 well-characterized dietary patterns: the alternate Mediterranean Diet, the alternate Healthy Eating Index, and the Fertility Diet, were not associated with risk of pregnancy loss.[34] Secondary analyses, however, suggested that the Fertility Diet, which was the same dietary pattern previously related to lower risk of anovulatory infertility, was inversely related to pregnancy loss in pregnancies occurring shortly after diet assessment.[34]

Gestational Diabetes Mellitus

The NHS II has also been used to address questions regarding the etiology and health consequences of common pregnancy complications with a strong focus on gestational diabetes mellitus (GDM), a common pregnancy complication defined as glucose intolerance with onset or first recognition during pregnancy. Before the work in NHS II, only prepregnancy overweight or obesity and cigarette smoking were well-documented risk factors of GDM. Sparse data on the role of diet and lifestyle factors were available.

Over the past decade, research based on NHS II data has identified a number of diet and lifestyle factors that are significantly associated with GDM risk.[35] Among these, potentially harmful factors include prolonged time of TV watching and Western dietary pattern.[35] Most recently, on the basis of NHS II data, NHS investigators identified that greater potato consumption was related to increased GDM risk. Potentially beneficial factors include regular physical activity—in particular, vigorous activity, brisk walking pace, stair climbing, the prudent dietary pattern (characterized by a high intake of fruit, green leafy vegetables, poultry, and fish), the Mediterranean diet pattern, and nut and fiber consumption.[6] Furthermore, findings from the NHS II data indicated that more than 45% of GDM might have been prevented if women adopted an overall healthy diet and lifestyle and maintained a healthy body weight before pregnancy.[6] Taken all together, NHS II findings demonstrated the important role of factors during the prepregnancy time window in the development of the common pregnancy complication.

Endometriosis

Endometriosis is a noncurable chronic gynecologic disease that affects around 10% of women.[7] Diagnosis requires surgical visualization of extrauterine endometrial lesions. Because of the invasive diagnosis for endometriosis, the majority of research on the disease had been restricted to case–control or cross-sectional studies restricted to infertile women undergoing surgical evaluation to rule out endometriosis as a cause of infertility or to women undergoing surgery for other purposes. By taking advantage of the high validity of self-reported surgically confirmed endometriosis among women in this cohort of nurses,[7] NHS II became the first prospective cohort to study endometriosis, providing novel and important etiological insights into this enigmatic and understudied disease. Previous estimates of endometriosis incidence relied on inpatient hospitalization records to classify endometriosis cases, which may underestimate disease burden by capturing only the most severe cases.

Research from this cohort was first to report endometriosis incidence estimates in a nationally representative sample and found that incidence of endometriosis occurred at an earlier age than previously reported.[7] This was also the first study to quantify heterogeneity in incidence of endometriosis and risk factor associations with endometriosis by diagnostic phenotypes, including pain presentation compared with copresentation with infertility.[8,9]

The NHS II has also altered thinking around endometriosis onset with a focus on risk across the life course. It was the first study to report inverse relationships between birth weight,[8] breastfeeding,[9] and diethylstilbestrol in utero exposure[8] with endometriosis risk. Although previous literature has been consistent regarding an inverse relationship between adult body size and endometriosis,[10] the NHS II was the first study to suggest that body size across the life course, as early as age 5 years, may influence risk.[7,10] The NHS II was also the first study to apply advanced nutritional methodology and to use longitudinal data to investigate the impact of diet across the life course on endometriosis risk that previously had been only evaluated in case–control studies. Research from the cohort has found an inverse relationship between dietary omega-3 fatty acids, total diary, low-fat dairy, thiamine, folate, vitamin C, vitamin E, circulating vitamin D, and a positive relationship with trans fat and risk of endometriosis.[11]

Uterine Leiomyomata

Uterine leiomyomata, commonly known as fibroids, are the most common tumor in women, with approximately 70% of women having evidence of a uterine leiomyoma over their lifetime. One in 4 women come to clinical attention for uterine leiomyomata with symptoms including pelvic pain, menstrual abnormalities, miscarriage, and pregnancy complications. Despite their frequency in the population, relatively little is known about the distribution and determinants of uterine leiomyomata.[36]

The NHS II has provided data central to our understanding of fibroid incidence and risk factors. NHS investigators described the increased incidence of uterine leiomyomata with increasing age among premenopausal women and, importantly, documented a 3-fold increase in UL risk for Black women compared with White women.[12] Because uterine leiomyomata are hormonally sensitive, regressing after menopause and hormone-suppressing therapy, reproductive factors have long been hypothesized to play a role in their development. The NHS II showed that an earlier age at first oral contraceptive use increases risk of uterine leiomyomata whereas later age at menarche, longer menstrual cycle length, parity, later age at first and last birth, shorter time since last birth, and breastfeeding decrease risk of uterine leiomyomata.[13]

The role of estrogenic effects in utero has also been evaluated in NHS II and other studies; a small but significant increase in risk of uterine leiomyomata with DES exposure is suggestive but needs to be balanced with a strong potential for detection and recall bias.[37,38] Increased adult body size was also shown to increase uterine leiomyomata risk and could also support a hormonal etiology to uterine leiomyomata development.[39]

The NHS II has also provided robust confirmation to previous retrospective and cross-sectional studies of an association between blood pressure and UL, reporting that women increased their risk between 8% and 10% with each 10 millimeters of mercury increase in diastolic blood pressure, regardless of antihypertensive therapy.[14] Other potential UL risk factors continue to be evaluated in NHS II, including a growing interest in the role of diet,[40] stress related to abuse or other acute or chronic exposures,[41] and environmental exposures such as air pollution.[42]

REPRODUCTIVE EVENTS AND CHRONIC DISEASE RISK

Although much of reproductive epidemiology focuses on fertility and optimal birth outcomes, 2 novel areas of investigation have been—and continue to be—pursued in the NHS. These involve the allied questions: What are the implications of reproductive events for the long-term health of the offspring and for the long-term health of the mother? The extended follow-up of women within these cohorts as they age as well as the availability of data across generations (through linkage with data collected from mothers and offspring of NHS II participants with the Growing Up Today Study [GUTS] cohort) has allowed NHS investigators to tackle these questions.

Birth Weight and Cardiometabolic Risk

The first question emerged from the "fetal origins hypothesis" promoted by David Barker in the United Kingdom. Barker's team had linked health visitor records from 1911 to 1930 in England to the national mortality register to show that low-birth-weight infants—long known to have elevated perinatal mortality—were also at increased risk for cardiovascular mortality in maturity. But these studies lacked data on social position, cigarette smoking, and other factors known to be linked to both fetal growth and cardiovascular risk.

Investigators in NHS I felt sure that they could explain the birth weight–mortality associations as a byproduct of confounding. However, when they used birth weight data recalled by the nurses and decades of longitudinal lifestyle data, they were unable to "explain away" the birth weight–cardiovascular disease association. In short, NHS data also showed that the smaller the woman was at birth, the higher her risk of cardiovascular disease, despite her social position, smoking habits, diet, family history of cardiovascular disease, or other risk factors.[15] Data from NHS I also showed that women born small had higher risks of hypertension[43] and type 2 diabetes,[44] and that the highest risk of coronary heart disease and stroke fell upon those who were born small but had gained more weight since childhood.[45] The implications of these findings are that cardiometabolic health may be "programmed" in the womb, or that the genes that determine fetal growth also affect vascular and metabolic disease.

Pregnancy Complications and Cardiometabolic Risk

These observations led to more questions. If the birth weight of the child predicts his or her risk of future disease, what does it portend for the future health of the mother? And what do other pregnancy complications, such as GDM, preeclampsia, or spontaneous preterm delivery, tell us about the mother's long-term health? Investigators are using data from NHS II to pursue these questions.

To date, NHS investigators have observed that women who have had pregnancies complicated by preeclampsia are at increased risk for hypertension, type 2 diabetes, and cardiovascular disease; women who have delivered preterm infants are at increased risk for type 2 diabetes[16]; and women with a history of GDM are at exceptionally increased risk for type 2 diabetes[17] and hypertension[18] later in life. As such, identifying determinants (i.e., genetic and nongenetic risk factors and the interactions of them) on the risk of progressing to type 2 diabetes and comorbidities among the high-risk women is pivotal for the early prevention of these chronic conditions. With a focus on women with a history of GDM, the ongoing Diabetes and Women's Health Study led by investigators from the National Institutes of Health and the NHS aims to address these questions and to better understand the early pathogenesis of type 2 diabetes. This work has identified that healthful dietary patterns,[19] physically active lifestyles,[20] and limited weight gain[21] after the index pregnancy were related to lower type 2 diabetes risk, whereas a low-carbohydrate, but high in animal fat and protein diet,[22] was related to an elevated risk of type 2 diabetes.

Long-Term Health Consequences of Other Reproductive Events

Similar ongoing work is also addressing the long-term health consequences of other reproductive events. Women with endometriosis may be at heightened risk for other chronic diseases later in life given the complex hormonal, inflammatory, and immunologic milieu that women with the disease experience. The NHS II was the first study to report a potential relationship of endometriosis with cardiovascular disease.[23] Research from the cohort has also supported

previous findings on endometriosis and increased risk of systemic lupus erythematosus and rheumatoid arthritis,[24] but now is rigorously assessing temporality, potential confounding, mediation, and misclassification biases.

The NHS II has also provided valuable insight regarding the health consequences of infertility treatment. Investigators from the NHS have found that the vast majority of infertile women used clomiphene citrate (94%), with a large majority of women reporting clomiphene as their only form of treatment (73%).[25] Among NHS II participants, history of infertility and use of fertility treatment was found not to increase risk of having a child with autism.[26] Investigators from NHS II were the first to investigate fertility treatment and subsequent hypertension risk, finding no association between them.[25]

TRANSGENERATIONAL RESEARCH

As fruitful as NHS I and NHS II have been to addressing hypotheses regarding the etiology of reproductive pathology, reproductive epidemiologists working with NHS data have continuously faced challenges related to the fact that reproductive events were not identified as primary outcomes from the outset. Key covariate data, such as data on pregnancy intention and data on exposures during pregnancy, were never collected or not systematically collected in these cohorts. Furthermore, collection of data on exposures of interest was never timed in relation to the reproductive events (such as a specific pregnancy or attempt to conceive) but rather in relation to chronologically timed follow-up cycles.

Most of those barriers are currently being removed in the ongoing NHS3. The use of personalized study timelines, including the introduction of substudies triggered by reproductive events such as pregnancy or pregnancy planning, including the ability to collect exposure and covariate information directly from male partners or fathers, has allowed us to expand the scope of reproductive research within the NHSs. In this ongoing work focused on fecundity, NHS investigators were able to revisit the question of adiposity and fecundity, this time allowing us to provide estimates of absolute delays in time to conception associated with recent body weight and with changes in body weight.

In a concerted effort to give back to the nursing community, NHS investigators have also devoted significant effort to evaluating the relation between occupational exposures and fecundity. Additional areas that have been substantially enhanced in NHS3 include more thorough assessments of PCOS and the assessment of temporally linked exposure information before, during, and after pregnancy. This focus on event-timed collection of exposure and outcome date for reproductive health investigation developed for NHS3 is also currently being incorporated into the continued follow-up of GUTS, the prospective cohort study of more than 25 000 offspring of NHS II participants who were recruited as children and, as of the writing of this article, have been followed for 20 years and are entering their peak reproductive years.

SUMMARY

Although the original goals of the NHS I and NHS II did not include the study of reproductive health per se, their assessment of reproductive events as covariates to address cancer-related hypotheses facilitated this research, which grew into an important component of NHS I and NHS II. Data from these cohorts have helped identify risk factors for infertility, pregnancy loss, GDM, endometriosis, and UL. In addition, they have allowed research evaluating how these and other reproductive life events have an impact on the risk of developing chronic noncommunicable diseases.

In recent years, the establishment of NHS3 and the continued follow-up of GUTS has expanded the scope of reproductive research and allowed for more refined assessment of reproductive events than was possible in NHS I and NHS II. These new resources, along with continued use of existing resources in NHS I and NHS II, including multigenerational linkages of related individuals across cohorts, will continue to be a valuable resource for investigators interested in reproduction as the NHSs move into their fifth decade, and will continue to help improve women's health from preconception through late adulthood and onto the next generation. AJPH

CONTRIBUTORS

All authors contributed to the conceptualization and design of the study. J. E. Chavarro drafted the article. All authors contributed to editing the article and approved it in its final form.

ACKNOWLEDGMENTS

The Nurses' Health Study (NHS) is supported by National Institutes of Health (NIH) grants UM1 CA186107, P01 CA87969, R01 CA49449, R01 HL034594, and R01 HL088521. The NHS II is supported by NIH grants UM1 CA176726 and R01 CA67262. The NHS3 and the Growing Up Today Study have also been supported by grants from the Breast Cancer Research Foundation. Specific work presented in this article was additionally supported by NIH grants 3R25CA057711, T32HD060454, P30 DK046200, R03 HD081064, R21 HD059955, R03 HD48544, R01 HD52473, and R01 HD57210, and NIH contract HHSN275201000020C. C. Zhang is supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH.

HUMAN PARTICIPANT PROTECTION

No protocol approval was necessary because this was a literature review.

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EDITOR'S NOTE

Because of space restrictions and the large volume of references relevant to the Nurses' Health Study, additional references are provided in a supplement to the online version of this article at http://www.ajph.org.