Psychiatric, Psychological, and Social Determinants of Health in the Nurses' Health Study Cohorts

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Objectives. To review the contribution of the Nurses' Health Studies (NHS) on factors that influence mental and physical health.

Methods. Narrative review of all published articles using data from the NHS, the NHS II, and the Growing Up Today Study focusing on mental health conditions (e.g., depression, posttraumatic stress disorder, anxiety) and psychosocial resources and stressors (e.g., job strain, interpersonal violence, social relationships, sexual orientation) between 1990 and 2016.

Results. Studies have considered a broad array of determinants (e.g., genes, biomarkers, air pollution) and consequent behavioral and disease-related outcomes (e.g., body weight, smoking, cardiometabolic diseases, cancer, autism). Findings suggest anxiety, posttraumatic stress disorder, childhood violence, caregiver burden, and job insecurity may increase the risk of coronary heart disease and diabetes, whereas findings with cancer are mixed. This work directly affects public health actions, as demonstrated by recent inclusion of a gender expression measure in state surveys.

Conclusions. The NHS cohorts have produced novel and influential research on the interplay of psychological and social factors with health. Psychological and social variables are important contributors to the maintenance or decline of physical and mental health. (*Am J Public Health.* 2016;106:1644–1649. doi:10.2105/AJPH.2016.303318)

See also Galea and Vaughan, p. 1531.

The Nurses' Health Study (NHS; 121 700 nurses aged 30–55 years in 1976) first biennial questionnaires gathered data on sociodemographic characteristics, contraceptive methods, medical conditions, nutrition, and health-relevant behaviors. Starting in 1988, measures of psychosocial factors were incorporated. Similarly, the Nurses' Health Study II (NHS II; 116 430 nurses aged 25–42 years in 1989) included psychosocial factors on questionnaires starting in 1993. In the Growing Up Today Study (GUTS; 16 882 children aged 9–14 years), offspring of NHS II participants completed items on medical conditions, lifestyle, self-perception, and sexuality since 1996. The expressed interest of the nurses and emerging research suggesting an important interplay between psychological, social, and biological processes motivated the assessment of psychosocial variables.[1–4]

Nearly 150 articles targeting psychological or social factors that examined these cohorts' data have been published to date. Prevalence rates of psychiatric conditions (e.g., anxiety, depression) and psychosocial stressors (e.g., sexual minorities and violence in adulthood) observed among NHS participants are generally comparable to those of the general population. Most studies used the prospective research design, but cross-sectional, retrospective, or case–control studies were also published.

Studies adjust for similar covariates, including demographics (e.g., age, education), health and medical factors (e.g., medical conditions, menopausal status, medication, body mass index), and lifestyle (e.g., tobacco and alcohol use, diet and exercise) as potential mediators or confounders. Medical conditions are either self-reported (e.g., hypertension), self-reported and validated by blinded physician (e.g., cancer), or extracted by blinded physicians from patient records (e.g., stroke). Deaths are reported by next of kin or postal authorities or found in a search of the National Death Index. Most studies assess the risk of disease onset or mortality (using hazard ratios [HRs], odds ratios [ORs], prevalence ratios [PRs], or relative risks [RRs]), and some examine changes over time (e.g., of behaviors).

We have presented published research that examined the NHS cohorts as we considered determinants of psychiatric conditions or psychosocial risk factors in relation to health. We gathered studies through PubMed and PsycInfo, and lead researchers of the NHS cohorts reviewed the list to ensure completeness. For the sake of parsimony, we have described only a few studies; a comprehensive report of all articles is available in a supplement to the online version of this article at http://www.ajph.org (Table A: psychiatric conditions; Table B: psychosocial resources and stressors). Because of space constraints, we have included factors with more limited findings (socioeconomic status, job strain, caregiving) in the tables only.

DETERMINANTS OF PSYCHIATRIC CONDITIONS AND EVENTS

Four major psychiatric conditions have been assessed and examined in the NHS cohorts.

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Depression

Over the past 2 decades, depressive symptoms were assessed approximately every 4 years with the 5-item Mental Health Index,[5] the 10-item Center for Epidemiologic Studies-Depression,[6] or the 15-item Geriatric Depression Scale,[7] depending on timing and age appropriateness. Antidepressant use and clinician-diagnosed depression were also ascertained on every biennial questionnaire. Studies addressing depression focus on either symptom burden or incident depression, where the latter generally takes a Boolean OR operator approach (self-reported clinician-diagnosed depression, antidepressant use, or severe depressive symptoms by published cutpoints), yielding prevalence rates comparable to those obtained with in-person evaluations.[8,9]

Numerous depression risk factors have been evaluated in the NHS cohorts, including long sleep duration, restless legs syndrome, urinary and fecal incontinence, psoriasis and psoriatic arthritis, and genetic factors. Identifying lifestyle factors as influencing risk of depression and considering bidirectionality have been novel contributions. For instance, among 50 739 women, there was a 20% lower 10-year risk of depression for those in the highest versus lowest categories of caffeine intake (Lucas 2011, Table A). This study garnered particular attention because few large-scale, rigorous investigations had evaluated the role of caffeine, one of the most consumed psychoactive substances worldwide, on depression risk. Moreover, women reporting 90 or more minutes versus less than 10 minutes per day of physical activity had a 20% lower depression risk; significant effects were also observed with intermediate levels of 30 or more minutes per day, supporting a public health message that even modest but regular physical activity may improve mental health. Women with versus those without type 2 diabetes mellitus were more likely to develop depression subsequently ($RR_{\text{fully adjusted}} = 1.29$; $n = 65\,381$), whereas those with higher versus those with lower depressive symptoms had 17% increased odds of type 2 diabetes onset (Pan 2010a). Considering a life course approach with younger participants has also provided important insights; the highest burden of first-onset depression occurs among adolescents and young adults.[10] Higher depressive symptoms risk was observed in girls with eating disorders (Sonneville 2013; Field 2012), children of mothers who reported severe childhood abuse (Roberts 2015a), and youths reporting early gender-nonconformity behaviors (Roberts 2013a).

Posttraumatic Stress Disorder

A supplemental screening questionnaire on trauma exposure and posttraumatic stress disorder (PTSD) symptoms was mailed in 2008 to a subgroup of NHS II women (completed by 54 282 women).[11,12] Included was a modified version of the Brief Trauma Questionnaire[13,14] to assess exposure to 15 traumatic events (e.g., natural disaster, unwanted sexual contact) at any point in one's lifetime. Additionally, the NHS II asked about PTSD symptom occurrence with respect to the worst traumatic event using the 7-item Short Screening Scale for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (Washington, DC; American Psychiatric Association; 1994) PTSD.[15] Subsequently, a telephone interview was conducted with a subsample of women who reported being exposed to at least 1 traumatic event ($n = 3013$) to provide a diagnostic measure of PTSD.[11] In 2007, GUTS participants completed a similar screen.[15]

Investigators have examined mainly the role of gender and sexual characteristics or genetic markers in predicting PTSD symptomatology. For example, among 9864 young adults, those who reported higher levels of gender-nonconforming behaviors during childhood had a significant 20% to 40% higher PTSD risk in early adulthood than did their peers (Roberts 2012a). With regard to genetic research, investigators conducted a PTSD association study ($n = 2538$; 845 PTSD cases 1693 controls) using 3742 single nucleotide polymorphisms across more than 300 genes (Solovieff 2014). Polygenic analyses showed that single nucleotide polymorphisms in the vesicular monoamine transporter 2 (*SLC18A2*) linked with mood disorders in other work were also significantly related to a higher PTSD risk (e.g., $OR_{rs363276} = 1.42$). Further studies revealed a positive association between polygenic risk scores for bipolar disorder and schizophrenia with PTSD risk (Sumner 2016) but null associations with 2 other candidate genes (i.e., *ADCYAP1R1* and *RORA* polymorphisms; Guffanti 2014; Chang 2012).

Anxiety

Anxiety symptoms were asked about twice approximately 12 years apart in NHS and NHS II using the validated self-report Crown-Crisp Index.[16,17] Although the 8-item scale focuses mostly on symptoms relevant to fear and phobia disorders such as panic disorder and agoraphobia (e.g., feeling panicky in crowds), it also incorporates worry-related items (e.g., worrying unduly when relatives are late coming home).

Anxiety onset has been considered in relation to novel determinants, such as toxic environmental exposures. For instance, using spatiotemporal prediction models on the basis of zip code geocode matching for 71 271 women, participants exposed to more versus less air pollution up to 15 years before anxiety assessment had a significant 9% to 15% increased odds of reporting clinical levels of anxiety symptoms (Power 2015). In another unconventional study, no overall association was evident among 599 women who underwent x-ray assessing fluorescence tibia or patella bone lead exposure and anxiety symptoms (Eum 2012). Other research indicated that whereas informal caregiving and body mass index were associated with higher anxiety levels subsequently (Cannuscio 2002; Walter 2015b), various polygenic scores and telomere length were not (Ramin 2015).

Suicide

Studies from the NHS cohorts data have contributed important insights to risk factors for the devastating outcome of suicide. With a view to prevention, these studies have focused on modifiable factors such as psychosocial stress, diet, and lifestyle.

For example, women with the highest versus those with the lowest levels of social integration had an approximately 80% lower suicide risk over 18 years of follow-up (Tsai 2015). Although current versus never smoking was linked to more than a 2 times higher suicide risk, former smoking was unrelated (Lucas 2013). Suicide risk also declined more with daily consumption

of caffeinated coffee (Kawachi 1996; Lucas 2014b).

PSYCHIATRIC CONDITIONS AS DETERMINANTS OF DISEASE

Investigators also considered 3 of the major psychiatric conditions as potential risk factors for diseases and other health consequences.

Depression

Findings with cardiometabolic outcomes have been highly consistent, demonstrating that depression is significantly associated with the onset of type 2 diabetes, cardiovascular disease (CVD), and mortality. For instance, depressive symptoms were related to 1.5 times higher fatal coronary heart disease (CHD) risk, and antidepressant use was associated with a more than 3 times sudden cardiac death risk (Whang 2009). With regard to cancer, results have been more mixed. Depressive symptoms were marginally related to colorectal cancer risk (Kroenke 2006), whereas neither clinician-diagnosed depression nor antidepressant use was related to incident breast cancer (Reeves 2015). Notably, one of the first studies considering depression and ovarian cancer in humans showed that women who were depressed (using the Boolean OR approach) at 2 consecutive time points versus those who were not depressed were 34% more likely to develop ovarian cancer (Huang 2015).

Limited work has been conducted on other outcomes, but a noteworthy bidirectional study among 65 955 NHS women showed that depression was related to a subsequent 38% higher odds of developing obesity, whereas baseline obesity was associated with an 11% higher odds of incident depression (Pan 2012a).

Posttraumatic Stress Disorder

Findings have consistently suggested that higher PTSD symptoms are associated with increased CVD, type 2 diabetes, and arthritis risk. Findings from NHS II are particularly valuable because they can distinguish the effects of the psychological sequelae of trauma (PTSD) from trauma exposure alone. For example, among 49 978 women followed over 20 years, compared with women who were not exposed to a prior trauma, those with the most PTSD symptoms had a 43% increased CVD risk, after controlling for traditional confounders (Sumner 2015). In this sample, adult health behaviors and medical determinants accounted for 14% of the association of trauma alone (no PTSD symptoms) and 47% of high PTSD symptoms with CVD onset (Sumner 2015). Effect magnitudes were similar after adjusting for depression, suggesting an independent effect of PTSD. Most previous work was conducted in military and male samples, and this study was one of the first to consider trauma-related factors with CVD onset in civilian women.

Some authors have suggested that autistic traits may result from experiencing PTSD. A novel intergenerational study tested this hypothesis and found a dose–response relationship between lifetime PTSD symptoms among women and risk of autism spectrum disorder in their offspring (e.g., $RR_{6–7symptoms} = 2.32$; Roberts 2014a). Other studies have explicitly tested whether PTSD leads to a greater likelihood of behavioral risk for chronic disease. For instance, 1 study found that all women with a prior trauma had significant weight gain over time, but the most rapid weight gain was evident for women with 4 or more PTSD symptoms (Kubzansky 2014).

Anxiety

Anxiety has been examined in relation to incident CHD risk among 72 359 women initially disease-free over 12 years (Albert 2005). In age-adjusted models, higher anxiety symptoms were associated with increased sudden cardiac death and fatal CHD risk (RRs ranging from 1.55 to 1.77), but not nonfatal myocardial infarction. Associations were attenuated in multivariate models including risk-related conditions (e.g., hypertension, type 2 diabetes) that may mediate the anxiety–CHD relationship. This study replicated previous results from male cohorts and was one of the first to identify the role of anxiety in CHD onset in women, whose rates of anxiety are twice as high as those of men. In these cohorts, higher anxiety was also associated with increased type 2 diabetes risk (Farvid 2014).

Investigators have considered anxiety in relation to cognitive performance and various biomarkers linked with higher chronic disease risk (e.g., adipokines, cytokines, telomere length). For instance, in one of the first large-scale investigations evaluating anxiety specifically rather than general distress in relation to late-life cognition among 16 351 stroke-free women, those reporting higher versus lower midlife anxiety levels performed worse on cognitive tasks completed 10, 12, and 14 years later (Okereke 2013).

PSYCHOSOCIAL RESOURCES AND STRESSORS AS DETERMINANTS OF HEALTH

A range of psychosocial factors have also been considered in relation to diseases and other health consequences.

Social Relationships

The NHS assessed the extent to which individuals are socially integrated 3 times at 4-year intervals with the Berkman–Syme Social Networks index,[18] which asked about participants' marital status, social network size, frequency of contact with social ties, attendance at religious services, and participation in other social groups. Additionally, the presence and extent of contact with a confidant was assessed in 1992 and 2000. To assess attachment, GUTS offspring (2005) and their NHS II mothers (2006) completed a 9-item scale, which correlates highly with more complex measures of relationship quality.[19,20]

Limited work has been conducted on disease and mortality risk. One study found that poor social integration was associated with a 66% increased risk of all-cause mortality and a 2 times higher risk of breast cancer mortality over 12 years of follow-up among 2835 women with breast cancer (Kroenke 2006; Table B). This study was noteworthy because it was the first to examine relationships reported before cancer diagnosis, and it assessed social support obtained from naturally occurring networks rather than from group interventions.

Social integration has shown protective effects on numerous psychological and behavioral outcomes. For instance, better quality of life and mental functioning was documented in breast cancer survivors (Michael 2002) and women experiencing

high-stress situations (Achat 1998). In a study examining the impact of marital status changes on concomitant changes in health behaviors, certain health-damaging (e.g., relapsing and starting to smoke, decreased vegetable intake) and health-promoting (e.g., weight loss, increased physical activity) changes were evident in women experiencing divorce or widowhood and remarriage (Lee 2005). Other findings demonstrated poorer physical functioning among women without a confidant (Michael 1999). In an innovative intergenerational study, medium and high mother–child attachment were associated with a lower likelihood of opioid use in 7646 children (Cerdá 2014).

Interpersonal Violence

In 2001, a violence questionnaire was administered to a subset of the NHS II cohort (n = 68 376). Specifically, physical abuse in childhood and adolescence was measured with a revised version of the validated Conflict Tactics Scale,[21] and sexual abuse items were adapted from an earlier national survey.[22,23] The frequency of experiencing physical and sexual abuse in adulthood (aged 18 years and older) was evaluated with 2 single items, respectively. The Women's Experiences with Battering Scale[24] assessed exposure to emotional violence in one's intimate relationship. In the GUTS, the frequency of past-year bullying was assessed in 2001 with items from the World Health Organization Health Behavior of School-Aged Children Survey.[25] The frequency of victimization behaviors experienced before aged 11 years was also measured in 2007 with validated relevant questionnaires (Roberts et al.[26] provides details).[21,27,28]

These cohorts' data led to the first large-scale prospective studies using a comprehensive violence assessment in relation to cardiometabolic outcomes. Women who did versus those who did not report physical or sexual abuse in childhood had a 12% to 28% increased type 2 diabetes risk over a 16-year follow-up (Rich-Edwards 2010). Likewise, high childhood violence exposure was related to a significantly increased gestational diabetes risk (Mason 2016) and a somewhat elevated risk of CVD events, with associations partially explained by lifestyle and medical confounders (Rich-Edwards 2012). Conversely, associations were null with multiple sclerosis onset (Riise 2011). In adulthood, repeated physical abuse and severe emotional abuse perpetrated by one's partner were associated with 6% and 24%, respectively, increased hypertension risk (Mason 2012), whereas violence, especially its psychological forms, was related to elevated type 2 diabetes risk (Mason 2013a).

Studies of these cohorts show adverse effects of violence on smoking, food addiction, alcohol use, body weight, and mental health symptomatology. Using the unique capacity to assess intergenerational effects, NHS researchers showed that children of severely abused mothers were more likely to smoke (OR = 1.40), be overweight (RR = 1.21), and be obese (RR = 1.45) throughout adolescence and early adulthood (Roberts 2014b). Comparably, women who reported early violence exposure had a higher risk of manifesting more autistic traits as adults (Roberts 2015c) and of having offspring with autism (Roberts 2013b). Furthermore, violence history was associated with sexual orientation minority status (Austin 2008), a higher risk of uterine fibroids (Boynton-Jarrett 2011), early age at menarche (Boynton-Jarrett 2013), and increased levels of inflammatory biomarkers (e.g., C-reactive protein, interleukin-6; Bertone-Johnson 2012).

Sexual Orientation and Gender Identity

In 1995, NHS II women characterized their sexual orientation and identity using a validated single item.[29] Starting in 1999, GUTS children answered a question adapted from the Minnesota Adolescent Health Survey[30] regarding their feelings of sexual attraction.[31] Drawing on an existing measure,[32] an index of structural stigma was also created for the GUTS (Hatzenbuehler et al.[33] provides more details). In both cohorts, the term "sexual minorities" is generally used to reference all categories except heterosexuality. The GUTS administered the Items from the Recalled Childhood Gender Identity/Gender Role Questionnaire[34] in 2005 and 2007 to assess gender conformity before age 11 years (e.g., roles taken in pretend play, feelings of femininity and masculinity).

One pioneering study (n = 90 823) found that sexual minorities were more likely to have risk-related conditions and behaviors associated with breast cancer (e.g., nulliparity, greater alcohol consumption) and CVD (e.g., overweight, smoking) than were their heterosexual counterparts (Case 2004). More recent work showed that lesbian and bisexual premenopausal women had 6% to 10% greater odds of breast cancer than did heterosexual women (Austin 2012), whereas no differences were observed for colon cancer risk (Austin 2014).

Numerous studies examined behavioral correlates of sexual and gender constructs, including diet and weight, exercise, indoor tanning, tobacco, and alcohol and drug use. For instance, young sexual minorities were more likely to use drugs than were heterosexuals, with greater usage among females than among males and in adolescence than in early adulthood (Corliss 2010). Other novel research suggested that some sexual minorities underutilized cancer screenings, routine reproductive health screenings, and birth control methods (Charlton 2011; Charlton 2013; Austin 2013; Charlton 2014). Being a sexual minority or reporting gender nonconformity was associated with a higher risk for PTSD and depression (Case 2004; Roberts 2012a, 2012b, 2013a), abuse (Roberts 2012a; Austin 2008), and bullying (Roberts 2012b; Berlan 2010) and a greater likelihood of transgender identity (Reisner 2014). Finally, considering less studied health-related outcomes, sexual minorities were more likely to report medically unexplained pain (Roberts 2013c), whereas gender nonconformity in the GUTS was associated with autistic traits exhibited by offspring and their mothers, as reported by NHS II women (Shumer 2015).

CONCLUSIONS

Since 1988, studies of NHS, NHS II, and GUTS cohorts have substantially contributed to the scientific understanding of the role of psychosocial variables in physical and mental health. These epidemiological cohorts have been among the few large-scale studies to collect detailed information on psychological and social factors in conjunction with rigorous assessment of behavior and health, with a multiple cohort structure providing opportunities for intergenerational projects. Most

studies have used the prospective research design and the strong participation rate of 90% throughout more than 2 decades of follow-up.[35] Having repeated measures available permits the investigation of temporal changes in health-related phenomena. The examination of bidirectional associations and the large sample sizes covering a broad age range facilitate more methodologically rigorous research on a wide spectrum of outcomes than was previously possible. Other strengths are the unique substudies incorporating novel exposures and mediators (e.g., biomarkers, PTSD) in which specific research questions can be examined in greater detail.

Many of these studies have provided pioneering findings and fostered important subsequent research. Articles are routinely published in high-impact journals, with more than 8200 citations to date, including many highly cited studies that have also been reported in the media. Although some scales used in these cohorts may be considered outdated by current standards, the results are congruent with findings from other (often smaller) studies with better validated measures and thus support the continued use of these older scales. Also worth noting is that the replication or extension of findings from studies using other measures or from different cohorts suggests that phenomena occurring among the relatively educated women and their children in the NHS cohorts are similar to those observed in more diverse populations. Finally, this work has also had a direct public health impact; for example, on the basis of GUTS findings, in 2012 the Centers for Disease Control and Prevention implemented the use of the gender expression measure[36,37] in state surveys monitoring adolescents' health.[38]

NHS research has increased our understanding of the determinants of mental health and of the interplay between social and psychological factors and physical health in women and their children. For instance, anxiety, PTSD, and, partly, childhood violence, caregiver burden, and job insecurity are significantly associated with a higher risk of incident CVD and, for the first 3 exposures, also with type 2 diabetes. By contrast, work focusing on cancer has revealed more mixed associations: depression was associated with a modest risk of ovarian and colorectal cancers but not with breast cancer; sexual minorities had an increased risk of breast cancer but not colon cancer, whereas job strain and caregiving were unrelated to breast cancer. Cancer is a heterogeneous disease with a multifactorial etiology and a progressive insidious onset, so determinants might be harder to identify.[39] Further work is thus warranted, especially on biobehavioral mechanisms that may lie on the pathway between psychosocial factors and carcinogenesis.

Importantly, the cohort data have facilitated a more systematic look into potential mechanisms by which psychosocial variables may influence disease, including inflammation, body mass index, and hypertension. Furthermore, the cohorts have shed light on the longstanding debate on whether anxiety and depressive symptoms are causes or consequences of lifestyle (e.g., diet, exercise) and body mass index by revealing bidirectional associations. Such results underline the importance of testing the extent to which psychosocial interventions aiming to improve emotional states truly influence subsequent health behaviors. Because most individuals fail to change unhealthy habits even knowing they impose risk for chronic illnesses,[40,41] psychosocial determinants of behaviors are potentially relevant targets for primary prevention. Future work should test the effectiveness of such interventions; if found successful, their implementation might reduce adverse behaviors and subsequently improve physical health.

Taking advantage of long-running and richly characterized cohorts, researchers from the Harvard studies have begun to disentangle the extent to which psychological and social variables may play a causal role in the maintenance and decline of physical health over the life course beyond conventional medical and behavioral determinants. There has been a great deal of work on the psychosocial determinants of behaviors and health since the first edition of the *Social Epidemiology* textbook in 2000.[42] NHS, NHS II, and GUTS prospective cohorts contributed to this exciting broadening of our understanding of health determinants. The pursuit of this work and the ability to take a life course perspective will provide greater insight into bidirectional associations, biobehavioral pathways, and intergenerational processes that may contribute to the interplay between psychosocial factors, mental health, and physical health, thereby guiding future interventions and public health policies. AJPH

CONTRIBUTORS

C. Trudel-Fitzgerald, O. I. Okereke, and L. D. Kubzansky conceptualized and designed the review, and critically revised the article. O. I. Okereke and L. D. Kubzansky are co-last authors. All authors interpreted the data and the cited studies and drafted the article.

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EDITOR'S NOTE

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