



Association of early life physical and sexual abuse with premature mortality among female nurses: prospective cohort study

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ABSTRACT

OBJECTIVE

To explore associations between early life physical and sexual abuse and subsequent risk of premature mortality (death before age 70 years).

DESIGN

Prospective cohort study.

SETTING

The Nurses' Health Study II (2001-19).

PARTICIPANTS

67 726 female nurses aged 37-54 years when completing a violence victimization questionnaire in 2001.

MAIN OUTCOME MEASURES

Hazard ratios and 95% confidence intervals for total and cause specific premature mortality by childhood or adolescent physical and sexual abuse, estimated by multivariable Cox proportional hazard models.

RESULTS

2410 premature deaths were identified over 18 years of follow-up. Nurses who experienced severe physical abuse or forced sexual activity in childhood and adolescence had a higher crude premature mortality rate than nurses without such abuse in childhood or adolescence (3.15 v 1.83 and 4.00 v 1.90 per 1000 person years, respectively). The corresponding age adjusted hazard ratios for premature deaths were 1.65 (95% confidence interval 1.45 to 1.87) and 2.04 (1.71 to 2.44), respectively, which were materially unchanged after further adjusting for personal characteristics and early life socioeconomic status (1.53, 1.35 to 1.74, and 1.80, 1.50 to 2.15, respectively). Cause specific analyses indicated that severe physical abuse was associated with a greater risk of mortality due to external causes of

injury and poisoning (multivariable adjusted hazard ratio 2.81, 95% confidence interval 1.62 to 4.89), suicide (3.05, 1.41 to 6.60), and diseases of the digestive system (2.40, 1.01 to 5.68). Forced sexual activity as a child and adolescent was associated with greater risk of mortality due to cardiovascular disease (2.48, 1.37 to 4.46), external injury or poisoning (3.25, 1.53 to 6.91), suicide (4.30, 1.74 to 10.61), respiratory disease (3.74, 1.40 to 9.99), and diseases of the digestive system (4.83, 1.77 to 13.21). The association of sexual abuse with premature mortality was stronger among women who smoked or had higher levels of anxiety during adulthood. Smoking, low physical activity, anxiety, and depression each explained 3.9-22.4% of the association between early life abuse and premature mortality.

CONCLUSION

Early life physical and sexual abuse could be associated with a greater risk of adult premature mortality.

Introduction

Reduction of premature mortality (death before age 70 years), one of the United Nations Sustainable Development Goals, is a major public health focus.¹ While the dramatic development of public health and medical treatment over the past several decades has led to a worldwide reduction in age adjusted mortality, premature mortality from non-communicable diseases, injuries, and suicide remains a leading public health challenge.² In the United States between 1999 and 2013, a surprising increase in premature mortality of 0.5% per year occurred among middle aged white women.^{1,3} To design effective preventive strategies and prioritize interventions, identifying the risk factors of premature mortality from non-communicable diseases, injuries, and suicides is urgently needed. Besides the well identified risk factors such as unhealthy lifestyles and mental disorders, growing evidence shows that adverse childhood experiences might increase the risk of premature mortality.

Early life abuse, including physical and sexual abuse, is a global public health issue because it is common and substantially contributes to child mortality, and has a range of long term health consequences in adulthood.^{4,5} In the US in 2020, the estimated total number of children who suffered from physical and sexual abuse was 101 961 and 57 963, respectively.⁶ Evidence has linked childhood or adolescent physical and sexual abuse to adult hypertension,⁷ suicide attempts,⁸ violence or criminal behaviors,⁹ type 2 diabetes,¹⁰ and cardiovascular diseases^{11,12} as a result

WHAT IS ALREADY KNOWN ON THIS TOPIC

Early life abuse is a global public health issue because it substantially contributes to child mortality and a wide range of long term consequences during adulthood

Individual and combined types of early life abuse are associated with a greater risk of total and injury related mortality during adulthood

WHAT THIS STUDY ADDS

Childhood and adolescent physical abuse and forced sexual activity were associated with a greater risk of premature mortality due to various causes (eg, external causes, suicide, and cardiovascular diseases)

Women reporting early life physical abuse and forced sexual activity might continue to be vulnerable to premature mortality, highlighting the importance of providing trauma informed care for those who have experienced child abuse

of changes in health behaviors, psychiatric function, and biological systems.^{13–15} Meanwhile, several population studies have shown that experiencing individual or combined types of abuse in early life is associated with a greater risk of total and injury related mortality in adulthood.^{16–22} However, the association of childhood or adolescent abuse with total and cause specific premature mortality remains unclear. More importantly, while numerous studies have associated early life abuse with adult risk of mental health conditions (eg, depression and anxiety)^{15–23} and adverse lifestyle patterns (eg, poorer diet, obesity, and smoking),^{24–25} no study has examined potential interactive and mediating roles of these factors. Therefore, we examined the associations of childhood and adolescent sexual and physical abuse with subsequent risk of total and cause specific premature mortality. We also explored possible interactions between early life abuse and adult anxiety, depression, and unhealthy lifestyle patterns and the potential mediating role of these factors among middle aged female nurses in the Nurses' Health Study II (NHSII).

Methods

Study population

The NHSII is an ongoing prospective cohort established in 1989 by recruiting 116 429 US female nurses aged 25–42 years without compensation. Nurses have been followed biennially thereafter regardless of their job types and employment status using mailed or electronic questionnaires that collect data on demographic and lifestyle characteristics and health outcomes. The response rate of each follow-up cycle exceeds 90%. We restricted the present study to female nurses who received the Lifetime Exposure to Violence Victimization Questionnaire (n=91 248) and provided data on early life exposure to violence victimization in 2001 (n=68 374; fig S1). We further excluded participants who had missing data on abuse exposure (n=648), leaving 67 726 participants for the current analysis (fig S1). Most age standardized characteristics were similar among included female nurses (n=67 726) and those excluded because of a lack of data on early life abuse (n=47 868; table S1). Study procedures were approved by the institutional review boards of Mass General Brigham and Harvard TH Chan School of Public Health (protocol No 2009-P-002375), and those of participating registries as required. The return of completed questionnaires indicates participants' consent.

Determination of early life abuse

In 2001, experiences of physical and sexual abuse were separately assessed for childhood (occurring before age 12 years) and adolescence (occurring between ages 12 and 17 years). Physical abuse by parents, step parents, or adult guardians was assessed by the Revised Conflict Tactics Scale,²⁶ which queried five specific acts of physical abuse (kick, bite or punch you; push, grab or shove you; choke or burn you; hit you with something that hurt your body; physically attack

you in some other way). Response options for each item included never, once, a few times, and more than a few times. Sexual abuse was measured using modified questions from the Sexual Experiences Survey: "Were you ever touched in a sexual way" or "forced into any sexual activity" by an adult or an older child?²⁷ Response options included never, once, or more than once. To create a summary measure of physical abuse, we used the principal components factor analysis with oblique (Promax) rotation and identified four physical abuse groups in NHSII: none, mild, moderate, and severe (table S2).²⁸ Likewise, NHSII participants were classified into four sexual abuse groups: none; sexual touching as a child or adolescent; forced sexual activity as a child or adolescent; and forced sexual activity as a child and adolescent (table S2).²⁸ Because both abuse experiences were highly correlated, we also used a summary measure of physical and sexual abuse based on a principal components factor analysis, which has been described in detail in our previous study.²⁸ In brief, NHSII participants were categorized into five groups by combining subtypes of physical and sexual abuse occurring in childhood and adolescence: no abuse, mild or moderate single type, mild multiple types or severe single type, moderate chronic or multiple types, and severe chronic or multiple types (table S2).²⁸

The summary measure of childhood physical and emotional abuse before age 12 years was also assessed using the Childhood Trauma Questionnaire short form,²⁹ which asked five questions: "People in my family hit me so hard that it left me with bruises and marks"; "The punishments seemed cruel"; "I was punished with a hard object (eg, belt, board, cord)"; "Someone in my family yelled and screamed at me"; and "People in my family said hurtful or insulting things to me". Response options for each item included never (0), rarely (1), sometimes (2), often (3), and very often (4). We calculated the total Childhood Trauma Questionnaire score across items and divided it into five categories.³⁰ The Childhood Trauma Questionnaire also assessed social support up to age 11 by a single question: "There was someone in my family who helped me feel that I was important or special".²⁹

Determination of premature mortality

Deaths were identified by searching state vital statistics records and the National Death Index, supplemented by reports from next of kin or the postal authorities, which were able to correctly identify >98% of the deaths by comparing them against medical records.³¹ Cause of death was determined by reviewing medical records, autopsy reports, or death certificates based on the International Classification of Diseases, eighth and ninth revisions. We classified participants into 19 major categories according to the Statistics Netherlands' Database, the US Public Health Service, and the National Center for Health Statistics (table S3).^{32–33} According to the definition from the World Health Organization, premature mortality was defined as death before age 70 years.^{34–35} The 107 nurses who

Table 1 | Age standardized characteristics in 2001 according to severity of early life physical and sexual abuse among 67 726 female nurses (Nurses' Health Study II, 2001-19)

Characteristics*	Severity of physical abuse				Severity of sexual abuse			
	None	Mild physical abuse	Moderate physical abuse	Severe physical abuse	None	Sexual touching as child or adolescent	Forced sexual activity as child or adolescent	Forced sexual activity as child and adolescent
Number	31 460	12 607	17 785	5874	45 008	15 045	5778	1895
Age (years), mean (SD)	46.8 (4.7)	46.9 (4.7)	46.9 (4.6)	47 (4.6)	46.8 (4.7)	46.9 (4.7)	46.9 (4.6)	47.1 (4.6)
White	29 932 (95.1)	11 941 (94.7)	16 380 (92.1)	5381 (91.6)	42 652 (94.8)	13 943 (92.7)	5339 (92.4)	1700 (89.7)
Parental highest education above high school	14 254 (45.3)	5571 (44.1)	7025 (39.5)	2152 (36.8)	20 005 (44.4)	6103 (40.7)	2233 (38.6)	661 (35.0)
Parents owned home at participant's birth	18 436 (58.6)	6988 (55.3)	9528 (53.6)	2827 (48.3)	25 582 (56.8)	8245 (54.9)	3031 (52.4)	921 (48.9)
Parents worked as a professional, manager, or executive at the participant's birth	10 673 (33.9)	4036 (31.9)	4953 (27.9)	1484 (25.4)	14 771 (32.8)	4362 (29.1)	1556 (26.9)	457 (24.3)
Age at menarche (years), mean (SD)	12.4 (1.4)	12.4 (1.4)	12.4 (1.4)	12.4 (1.5)	12.4 (1.4)	12.3 (1.4)	12.3 (1.5)	12.2 (1.6)
Body mass index								
<18.5	409 (1.3)	160 (1.3)	210 (1.2)	61 (1.1)	623 (1.4)	147 (1.0)	42 (0.7)	28 (1.5)
18.5-24.9	15 633 (49.7)	6204 (49.1)	8115 (45.7)	2448 (42.0)	22 454 (49.8)	6778 (45.3)	2504 (43.3)	664 (35.3)
25-29.9	8448 (26.9)	3416 (27.1)	4985 (28.0)	1572 (26.7)	12 076 (26.9)	4174 (27.7)	1621 (28.1)	550 (29.0)
≥30	6970 (22.2)	2827 (22.5)	4475 (25.1)	1793 (30.3)	9855 (21.9)	3946 (26.1)	1611 (27.8)	653 (34.2)
Parental history of CVD before age 60 years	8524 (27.1)	3446 (27.4)	5105 (28.7)	1911 (32.3)	12 143 (27.1)	4384 (29.0)	1789 (30.9)	670 (35.0)
Total physical activity (hours/week), mean (SD)	2.4 (3.1)	2.5 (3.1)	2.4 (3.3)	2.5 (3.6)	2.5 (3.2)	2.3 (3.2)	2.4 (3.3)	2.4 (3.6)
AHEI-2010 dietary score,† mean (SD)	55.6 (12.8)	56.1 (12.7)	56 (12.9)	56.8 (13.1)	55.8 (12.8)	56.3 (12.9)	56.2 (13)	55.8 (12.7)
Alcohol intake (g/day), mean (SD)	3.8 (6.9)	4.5 (7.8)	4.0 (7.5)	4.2 (8.0)	4.0 (7.2)	4.2 (7.6)	4.1 (7.7)	3.6 (7.5)
Parity,‡ mean (SD)	1.9 (1.2)	1.9 (1.2)	1.9 (1.2)	1.8 (1.2)	1.9 (1.2)	1.9 (1.2)	1.9 (1.2)	1.8 (1.3)
Depression	7735 (24.6)	3730 (29.6)	5892 (33.1)	2738 (46.5)	11 656 (25.9)	5140 (34.1)	2350 (40.7)	949 (50.1)
Phobic anxiety symptom scores ≥3	7163 (22.8)	3327 (26.4)	4886 (27.5)	1982 (33.7)	10 934 (24.3)	3902 (25.9)	1821 (31.5)	701 (36.9)
Smoking status								
Never	22 043 (70.0)	7929 (62.8)	11 163 (62.8)	3184 (54.5)	30 600 (67.9)	9465 (63.1)	3184 (55.1)	1070 (56.6)
Past	7219 (23.0)	3512 (28.0)	5005 (28.1)	1936 (32.7)	10 957 (24.4)	4271 (28.2)	1880 (32.5)	564 (29.6)
Current 1-34 cigarettes/day	2069 (6.6)	1097 (8.7)	1498 (8.4)	708 (12.1)	3233 (7.2)	1221 (8.1)	679 (11.8)	239 (12.6)
Current ≥35 cigarettes/day	100 (0.3)	59 (0.5)	88 (0.5)	43 (0.7)	163 (0.4)	75 (0.5)	31 (0.5)	21 (1.1)
Oral contraceptive use								
Never	2805 (8.9)	1124 (8.8)	1447 (8.2)	420 (7.4)	4048 (8.9)	1184 (8.2)	446 (7.7)	118 (6.3)
Past	24 024 (76.4)	9812 (78.0)	14 109 (79.3)	4731 (80.3)	34 396 (76.5)	11 967 (79.3)	4728 (81.8)	1585 (83.6)
Current	4478 (14.3)	1618 (12.8)	2145 (12.0)	677 (11.5)	6341 (14.1)	1827 (12.1)	574 (9.9)	176 (9.3)
Tier of residence at birth,§								
North	6528 (20.7)	2383 (18.9)	3759 (21.1)	1138 (19.4)	9116 (20.2)	3141 (20.9)	1151 (19.9)	400 (21.1)
Middle	7821 (24.9)	3024 (24.0)	4536 (25.5)	1393 (23.7)	10 716 (23.8)	4035 (26.8)	1502 (26.0)	521 (27.4)
South	13 922 (44.3)	5867 (46.6)	7555 (42.5)	2632 (44.7)	20 611 (45.8)	6162 (40.8)	2443 (42.3)	760 (40.3)
Outside of US or uncertain	3189 (10.1)	1333 (10.6)	1935 (10.9)	711 (12.2)	4565 (10.1)	1707 (11.4)	682 (11.8)	214 (11.3)

AHEI-10=Alternative Health Eating Index 2010; CVD=cardiovascular disease; SD=standard deviation.

*Values are numbers (percentages) unless stated otherwise; means (standard deviations) and percentages of all variables except for age are age standardized.

†551 (0.8%) nurses had missing data on baseline diet scores (including alcohol intake).

‡Pregnancies lasting at least six months.

§The north tier of states, lying above 41-42° N latitude, includes states in the east column, the central column, the mountain column, and the Pacific column; the middle tier of states has east, central, mountain, and Pacific columns; the south tier, lying south of 37° N latitude comprises states in the east, central, mountain, and Pacific columns.

died at or after 70 years of age were treated as censored observations for which the event of interest was not observed during follow-up.

Assessment of covariates

Factors in early childhood, including race and ethnicity, age at menarche, parental highest education, home ownership, and profession at the time of the participant's birth, and the location of birth, were self-reported at baseline or during follow-up. Participants' body shape at age 5 years was assessed using somatograms (a set of nine drawings ranging from very lean to obese) and was shown to be reliable

for assessing childhood body mass index in a previous study.³⁶ Parity (number of pregnancies lasting at least six months) was collected at baseline and updated every two years until 2009 when most nurses had passed their reproductive lifespan. Adulthood cardiovascular disease risk factors (eg, physical activity, diet, smoking status, and alcohol intake), prescription drug use, and depression that might modify the influence of early life abuse were also collected biennially. Body mass index was calculated using baseline height and updated weight for each follow-up cycle. In 1991, 1995, 1999, 2003, 2007, 2011, and 2015, nurses reported how often, on average, they consumed a

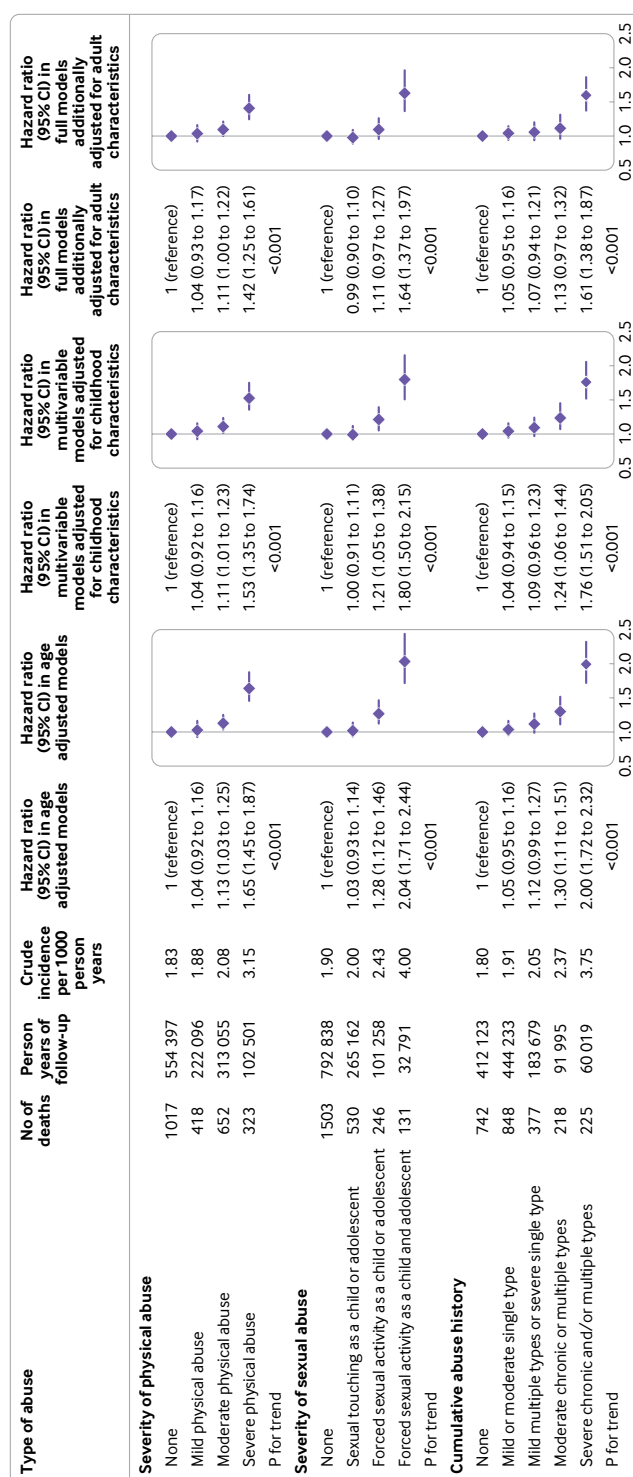


Table 2 | Risk of cause specific premature mortality (before age 70 years) with at least 40 deaths attributed according to the severity of physical abuse during childhood or adolescence among 67 726 female nurses (Nurses' Health Study II, 2001-19)

Cause specific mortality	Severity of physical abuse				P for trend‡
	None	Mild	Moderate	Severe	
Cancer					
Events/crude incidence per 1000 person years	393/0.71	175/0.79	221/0.71	85/0.83	—
Multivariable models adjusted for childhood characteristics*	1.00 (reference)	1.12 (0.93 to 1.34)	0.98 (0.83 to 1.15)	1.04 (0.82 to 1.31)	0.97
Full models additionally adjusted for adult characteristics†	1.00 (reference)	1.14 (0.95 to 1.37)	1.00 (0.85 to 1.18)	1.04 (0.82 to 1.31)	0.86
Cardiovascular disease					
Events/crude incidence per 1000 person years	68/0.12	19/0.09	51/0.16	16/0.16	—
Multivariable models adjusted for childhood characteristics*	1.00 (reference)	0.70 (0.42 to 1.17)	1.29 (0.89 to 1.85)	1.08 (0.62 to 1.87)	0.30
Full models additionally adjusted for adult characteristics†	1.00 (reference)	0.70 (0.42 to 1.17)	1.29 (0.89 to 1.87)	0.92 (0.53 to 1.62)	0.51
External causes of injury and poisoning					
Events/crude incidence per 1000 person years	36/0.06	14/0.06	24/0.08	20/0.19	—
Multivariable models adjusted for childhood characteristics*	1.00 (reference)	0.95 (0.51 to 1.77)	1.10 (0.66 to 1.86)	2.81 (1.62 to 4.89)	0.007
Full models additionally adjusted for adult characteristics†	1.00 (reference)	0.93 (0.50 to 1.73)	1.06 (0.63 to 1.79)	2.45 (1.40 to 4.29)	0.02
Senility and ill-defined diseases					
Events/crude incidence per 1000 person years	39/0.07	10/0.05	28/0.09	12/0.12	—
Multivariable models adjusted for childhood characteristics*	1.00 (reference)	0.69 (0.34 to 1.39)	1.31 (0.80 to 2.13)	1.46 (0.75 to 2.84)	0.17
Full models additionally adjusted for adult characteristics†	1.00 (reference)	0.73 (0.36 to 1.48)	1.30 (0.79 to 2.14)	1.27 (0.64 to 2.51)	0.28
Suicide					
Events/crude incidence per 1000 person years	17/0.03	7/0.03	14/0.04	11/0.11	—
Multivariable models adjusted for childhood characteristics*	1.00 (reference)	1.00 (0.41 to 2.41)	1.45 (0.71 to 2.96)	3.05 (1.41 to 6.60)	0.01
Full models additionally adjusted for adult characteristics†	1.00 (reference)	1.02 (0.42 to 2.52)	1.52 (0.74 to 3.13)	2.80 (1.26 to 6.22)	0.02
Respiratory disease					
Events/crude incidence per 1000 person years	18/0.03	11/0.05	12/0.04	8/0.08	—
Multivariable models adjusted for childhood characteristics*	1.00 (reference)	1.55 (0.73 to 3.29)	1.15 (0.55 to 2.39)	2.08 (0.89 to 4.83)	0.19
Full models additionally adjusted for adult characteristics†	1.00 (reference)	1.41 (0.65 to 3.04)	1.02 (0.49 to 2.15)	1.73 (0.73 to 4.08)	0.40
Diseases of the digestive system					
Events/crude incidence per 1000 person years	16/0.03	7/0.03	11/0.04	8/0.08	—
Multivariable models adjusted for childhood characteristics*	1.00 (reference)	1.15 (0.47 to 2.80)	1.16 (0.53 to 2.50)	2.40 (1.01 to 5.68)	0.12
Full models additionally adjusted for adult characteristics†	1.00 (reference)	0.97 (0.38 to 2.44)	0.95 (0.43 to 2.10)	1.83 (0.75 to 4.48)	0.39

Data are hazard ratios (95% confidence intervals).

*Model adjusted for age (continuous), white race or ethnicity (no or yes), body shape at age 5 (somatogram figure 1, 2, 3, 4, or ≥5), age at menarche (continuous), parental highest education (less than high school, completed high school, or more than high school), parents owned a home during infancy (no or yes), parents worked as a professional, manager, or executive during infancy (no or yes), the tier of birth (north, middle, south, or outside of United States or uncertain).

†Based on multivariable models with further adjustment for time varying body mass index (<24.9, 25-29.9, 30-34.9, or ≥35), smoking status (never, former, current 1-34 cigarettes/day, or current ≥35 cigarettes/day), parity (≤1, 2, or ≥3), Alternative Healthy Eating Index 2010 dietary score (five categories), alcohol intake (0, 1-14, or ≥15 g/day), oral contraceptive use (never, past, or current), menopausal status (premenopausal, postmenopausal, or uncertain), and postmenopausal hormone use (never, past, or current).

‡P for trend was conducted by modeling the categories of increasing severity of physical abuse as an ordinal level variable using integer values.

specified amount of nearly 130 food items over the previous year using a validated semiquantitative food frequency questionnaire. We calculated adherence to the Alternative Health Eating Index 2010 to reflect each nurse's overall diet quality.³⁷ In 1989, 1991, 1997, 2001, 2005, 2009, and 2013, a validated questionnaire was used to collect nurses' weekly hours of moderate to vigorous activities requiring at least three metabolic equivalent units per hour (eg, jogging, hiking, running, swimming, bicycling, playing racquetball or tennis, and performing calisthenics).³⁸ Clinician diagnosed depression was self-reported biennially since 2003.³⁹ Phobic anxiety, characterized by an excessive and irrational fear of an object, activity, or specific situations (eg, enclosed spaces, heights, or crowds), was assessed by the Crown-Crisp index that was calculated from eight questions administered in 1993 and 2005.⁴⁰ Most of these self-reported covariates have been validated in NHSII or NHS.⁴¹⁻⁴⁵

Statistical analysis

All analyses were conducted using the Statistical Analysis System, version 9.4 (SAS Institute). We used Cox proportional hazards models with time varying age and calendar time (in two year intervals) as the

underlying timescale to estimate hazard ratios and 95% confidence intervals for total and cause specific premature mortality according to early life physical and sexual abuse. Person years of follow-up started from the return date of the 2001 questionnaire until the date of death or end of follow-up (30 June 2019), whichever occurred first.

In the primary analysis, we included the following covariates as potential confounders, including white race or ethnicity, body shape at age 5, age at menarche, parental highest education at participant's birth, parents owned home at participant's birth, parents worked as a professional, manager, or executive at participant's birth, and the tier of birth. In a secondary analysis, we further adjusted for time varying adult characteristics, including body mass index, parity, smoking status, Alternative Healthy Eating Index 2010 dietary score, alcohol intake, menopausal status, oral contraceptive use, and postmenopausal hormone use. For the covariates with missing values, data from the most recent previous survey cycle were carried forward; otherwise, we created missing indicators (<1% for diet), which have been validated to induce minimal or no bias.⁴⁶

We further estimated the risk of premature mortality according to the joint categories of early

Table 3 | Risk of cause specific premature mortality (before age 70 years) with at least 40 deaths attributed according to severity of sexual abuse during childhood or adolescence among 67 726 female nurses (Nurses' Health Study II, 2001-19)

	Severity of sexual abuse				
Cause specific mortality	None	Sexual touching as a child or adolescent	Forced sexual activity as a child or adolescent	Forced sexual activity as a child and adolescent	P for trend†
Cancer					
Events/crude incidence per 1000 person years	576/0.73	181/0.68	91/0.90	26/0.79	—
Multivariable models adjusted for childhood characteristics*	1.00 (reference)	0.91 (0.77 to 1.07)	1.17 (0.94 to 1.46)	0.93 (0.62 to 1.38)	0.82
Full models additionally adjusted for adult characteristics†	1.00 (reference)	0.92 (0.78 to 1.09)	1.14 (0.91 to 1.43)	0.92 (0.62 to 1.37)	0.89
Cardiovascular disease					
Events/crude incidence per 1000 person years	95/0.12	31/0.12	15/0.15	13/0.40	—
Multivariable models adjusted for childhood characteristics*	1.00 (reference)	0.85 (0.56 to 1.28)	1.09 (0.63 to 1.89)	2.48 (1.37 to 4.46)	0.07
Full models additionally adjusted for adult characteristics†	1.00 (reference)	0.81 (0.54 to 1.22)	0.93 (0.53 to 1.62)	2.03 (1.11 to 3.72)	0.30
External causes of injury and poisoning					
Events/crude incidence per 1000 person years	53/0.07	20/0.08	13/0.13	8/0.24	—
Multivariable models adjusted for childhood characteristics*	1.00 (reference)	1.08 (0.64 to 1.81)	1.84 (1.00 to 3.40)	3.25 (1.53 to 6.91)	0.002
Full models additionally adjusted for adult characteristics†	1.00 (reference)	1.04 (0.62 to 1.74)	1.60 (0.86 to 2.98)	2.68 (1.24 to 5.79)	0.02
Senility and ill-defined diseases					
Events/crude incidence per 1000 person years	63/0.08	16/0.06	5/0.05	5/0.15	—
Multivariable models adjusted for childhood characteristics*	1.00 (reference)	0.73 (0.42 to 1.26)	0.61 (0.24 to 1.52)	1.61 (0.64 to 4.03)	0.68
Full models additionally adjusted for adult characteristics†	1.00 (reference)	0.72 (0.41 to 1.25)	0.46 (0.18 to 1.19)	1.46 (0.57 to 3.71)	0.38
Suicide					
Events/crude incidence per 1000 person years	29/0.04	9/0.03	5/0.05	6/0.18	—
Multivariable models adjusted for childhood characteristics*	1.00 (reference)	0.89 (0.42 to 1.88)	1.15 (0.44 to 2.99)	4.30 (1.74 to 10.61)	0.04
Full models additionally adjusted for adult characteristics†	1.00 (reference)	0.93 (0.43 to 2.00)	1.08 (0.41 to 2.84)	3.71 (1.45 to 9.48)	0.07
Respiratory disease					
Events/crude incidence per 1000 person years	25/0.03	10/0.04	9/0.09	5/0.15	—
Multivariable models adjusted for childhood characteristics*	1.00 (reference)	1.03 (0.49 to 2.15)	2.42 (1.12 to 5.24)	3.74 (1.40 to 9.99)	0.004
Full models additionally adjusted for adult characteristics†	1.00 (reference)	0.96 (0.45 to 2.02)	1.95 (0.88 to 4.30)	3.11 (1.12 to 8.67)	0.02
Diseases of the digestive system					
Events/crude incidence per 1000 person years	21/0.03	10/0.04	6/0.06	5/0.15	—
Multivariable models adjusted for childhood characteristics*	1.00 (reference)	1.38 (0.64 to 2.93)	2.12 (0.85 to 5.30)	4.83 (1.77 to 13.21)	0.003
Full models additionally adjusted for adult characteristics†	1.00 (reference)	1.31 (0.60 to 2.85)	1.73 (0.67 to 4.50)	4.53 (1.58 to 12.96)	0.01

Data are hazard ratios (95% confidence intervals).

*Model adjusted for age (continuous), white race or ethnicity (no or yes), body shape at age 5 (somatogram figure 1, 2, 3, 4, or ≥5), age at menarche (continuous), parental highest education (less than high school, completed high school, more than high school), parents owned a home during infancy (no or yes), parents worked as a professional, manager, or executive during infancy (no or yes), the tier of birth (north, middle, south, or outside of United States or uncertain).

†Based on multivariable models with further adjustment for time varying body mass index (<24.9, 25-29.9, 30-34.9, or ≥35), smoking status (never, former, current 1-34 cigarettes/day, or current ≥35 cigarettes/day), parity (≤1, 2, or ≥3), Alternative Healthy Eating Index 2010 dietary score (five categories), alcohol intake (0, 1-14, or ≥15 g/day), oral contraceptive use (never, past, or current), menopausal status (premenopausal, postmenopausal, or uncertain), and postmenopausal hormone use (never, past, or current).

‡P for trend was conducted by modeling the categories of increasing severity of sexual abuse as an ordinal level variable using integer values.

life physical abuse, sexual abuse, and social support. We also conducted stratified analysis according to adult body mass index (<25 v ≥25), smoking (never v ever), diet quality (the top 40% v the bottom 60%), physical activity (≥30 v <30 min/day), phobic anxiety symptom scores (<3 v ≥3), and depression (no v yes). Multiplicative interaction between these psychological and lifestyle factors and abuse experiences was evaluated by conducting the Wald test after adding interaction terms into multivariable models.⁴⁷ The additive interaction was estimated by calculating the relative excess risk due to interaction (RERI).^{47 48} We also explored to what extent these factors mediated the association between early life abuse and premature

mortality using a mediation analysis developed by Lin and colleagues.^{49 50} Finally, we conducted a series of sensitivity analyses to assess the influence of other potential confounding factors (pack years of smoking and the presence of other early life abuse), selection bias (the inclusion of nurses reporting cardiovascular diseases or cancer in 2001), and alternative definitions of mortality (deaths at any ages or before age 65 years).

Patient and public involvement

Patients and the public are not invited to comment on the study design, develop patient relevant outcomes, interpret the results, or write or edit the manuscript. However, participants are invited to provide

Table 4 | Risk of all cause premature mortality (before age 70 years) according to early life physical and sexual abuse among 67 726 female nurses stratified by psychological and lifestyle factors (Nurses' Health Study II, 2001-19)*

Stratified factors	Physical abuse		Forced sexual activity	
	None or mild	Moderate or severe	Never	Ever
Diet quality				
Top 40% (n=814 deaths)	1.00 (reference)	1.58 (1.30 to 1.93)	1.00 (reference)	1.42 (1.17 to 1.71)
Bottom 60% (n=1596 deaths)	1.00 (reference)	1.42 (1.22 to 1.64)	1.00 (reference)	1.33 (1.16 to 1.52)
P for multiplicative interaction	0.21	—	0.28	—
P for additive interaction	0.92	—	0.94	—
RERI (95% CI)	0.02 (−0.43 to 0.47)	—	0.02 (−0.37 to 0.40)	—
Proportion mediated by low diet quality	<0.1%	—	<0.1%	—
Smoking status				
Never (n=1239 deaths)	1.00 (reference)	1.36 (1.13 to 1.63)	1.00 (reference)	1.08 (0.90 to 1.29)
Current or past (n=1171 deaths)	1.00 (reference)	1.42 (1.22 to 1.66)	1.00 (reference)	1.46 (1.26 to 1.68)
P for multiplicative interaction	0.62	—	0.009	—
P for additive interaction	0.11	—	<0.001	—
RERI (95% CI)	0.33 (−0.08 to 0.74)	—	0.63 (0.28 to 0.98)	—
Proportion mediated by smoking	12.9% (9.1% to 18.0%)	—	16.2% (10.8% to 23.5%)	—
Body mass index				
<25 (n=944 deaths)	1.00 (reference)	1.68 (1.38 to 2.04)	1.00 (reference)	1.39 (1.15 to 1.68)
≥25 (n=1466 deaths)	1.00 (reference)	1.39 (1.19 to 1.61)	1.00 (reference)	1.34 (1.17 to 1.54)
P for multiplicative interaction	0.09	—	0.70	—
P for additive interaction	0.09	—	0.65	—
RERI (95% CI)	−0.32 (−0.69 to 0.05)	—	−0.07 (−0.38 to 0.24)	—
Proportion mediated by overweight or obesity	<0.1%	—	<0.1%	—
Physical activity				
≥30 min/day (n=750 deaths)	1.00 (reference)	1.43 (1.14 to 1.79)	1.00 (reference)	1.40 (1.14 to 1.72)
<30 min/day (n=1660 deaths)	1.00 (reference)	1.47 (1.28 to 1.69)	1.00 (reference)	1.29 (1.13 to 1.47)
P for multiplicative interaction	0.82	—	0.40	—
P for additive interaction	0.10	—	0.71	—
RERI (95% CI)	0.38 (−0.07 to 0.83)	—	0.08 (−0.33 to 0.48)	—
Proportion mediated by physically inactive	3.9% (2.7% to 5.7%)	—	7.3% (4.9% to 10.9%)	—
Phobic anxiety symptom scores				
<3 (n=1677 deaths)	1.00 (reference)	1.44 (1.24 to 1.68)	1.00 (reference)	1.18 (1.02 to 1.37)
≥3 (n=733 deaths)	1.00 (reference)	1.45 (1.19 to 1.76)	1.00 (reference)	1.55 (1.30 to 1.85)
P for multiplicative interaction	0.91	—	0.008	—
P for additive interaction	0.51	—	0.002	—
RERI (95% CI)	0.13 (−0.26 to 0.53)	—	0.54 (0.19 to 0.89)	—
Proportion mediated by anxiety	4.7% (2.8% to 7.7%)	—	5.9% (3.5% to 9.9%)	—
Depression				
No (n=1557 deaths)	1.00 (reference)	1.32 (1.11 to 1.56)	1.00 (reference)	1.27 (1.09 to 1.47)
Yes (n=853 deaths)	1.00 (reference)	1.43 (1.20 to 1.69)	1.00 (reference)	1.31 (1.11 to 1.54)
P for multiplicative interaction	0.74	—	0.91	—
P for additive interaction	0.20	—	0.35	—
RERI (95% CI)	0.27 (−0.14 to 0.67)	—	0.18 (−0.19 to 0.54)	—
Proportion mediated by depression	20.7% (14.4% to 28.9%)	—	22.4% (14.7% to 32.7%)	—

Data are adjusted hazard ratios (95% confidence intervals).

RERI=relative excess risk due to interaction.

*Model adjusted for age (continuous), white race or ethnicity (no or yes), body shape at age 5 (somatogram figure 1, 2, 3, 4, or ≥5), age at menarche (continuous), parental highest education (less than high school, completed high school, or more than high school), parents owned a home during infancy (no or yes), parents worked as a professional, manager, or executive during infancy (no or yes), and the tier of birth (north, middle, south, or outside of United States or uncertain).

constructive feedback on biennial questionnaires across follow-up, which has been incorporated when appropriate. The study has also incorporated suggestions from an internal review panel.

Results

Among 67 726 female nurses included in the current analysis, during childhood or adolescence, 46.5% (31 460 of 67 726) never experienced physical abuse and 66.5% (45 008 of 67 726) never experienced sexual abuse (table 1). Compared with nurses reporting physical or sexual abuse during childhood or adolescence, those without early life abuse were more likely to have parents who received higher education, owned a home, and worked as professionals, managers, or executives during

nurses' infancy (table 1). Additionally, depression, anxiety, smoking, obesity, and parental history of cardiovascular disease before age 60 years were less common among nurses who never experienced early life physical or sexual abuse (table 1).

Over 18 years of follow-up, 2410 deaths before the age of 70 occurred, including 874 from cancer, 154 from cardiovascular disease, 94 from external causes of injury and poisoning, 49 from suicide, and 49 from respiratory disease (table S3). Nurses who as a child and also an adolescent experienced severe physical abuse or forced sexual activity had a higher crude total premature mortality rate during follow-up than nurses without such abuse in childhood or adolescence (3.15 v 1.83 and 4.00 v 1.90 per 1000 person years,

respectively; fig 1). The corresponding age adjusted hazard ratios for total premature mortality were 1.65 (95% confidence interval 1.45 to 1.87) and 2.04 (1.71 to 2.44), respectively, which were materially unchanged after further adjusting for childhood covariates (1.53, 1.35 to 1.74, and 1.80, 1.50 to 2.15, respectively; fig 1). The increased total premature mortality risk persisted among nurses simultaneously reporting physical and sexual abuse in both periods (before age 12 years and at age 12-17 years; table S4). A similar pattern of association was observed across the summary categories of increasing severity and chronicity of physical and sexual abuse (fig 1). In the adjusted models, there was a 4% (95% confidence interval of hazard ratios 0.94 to 1.15) greater risk of total premature mortality for nurses reporting one episode of mild or moderate abuse, 9% (0.96 to 1.23) for mild multiple or severe single type of abuse, 24% (1.06 to 1.44) for moderate chronic or multiple types of abuse, and 76% (1.51 to 2.05) for severe chronic or multiple types of abuse compared with those without physical or sexual abuse. Further adjustment for adult covariates, many of which might be considered intermediates on the pathway between child abuse and adult mortality, only slightly weakened these associations (fig 1 and table S4). We also observed an increased risk of total premature mortality among nurses who had higher physical and emotional abuse and those who received rare or no social support during childhood (table S4).

When we examined specific premature mortality causes with at least 40 deaths (table 2 and table 3), severe physical abuse was associated with a greater risk of mortality due to external causes of injury and poisoning (hazard ratio 2.81, 95% confidence interval 1.62 to 4.89), suicide (3.05, 1.41 to 6.60), and diseases of the digestive system (2.40, 1.01 to 5.68) with adjustment for childhood covariates; forced sexual activity as a child and an adolescent was associated with a greater risk of mortality due to cardiovascular disease (2.48, 1.37 to 4.46), external causes (3.25, 1.53 to 6.91), suicide (4.30, 1.74 to 10.61), respiratory disease (3.74, 1.40 to 9.99), and diseases of the gastrointestinal system (4.83, 1.77 to 13.21). Severe chronic or multiple types of abuse were associated with a greater risk of mortality due to cardiovascular diseases (1.98, 1.14 to 3.43), external causes of injury and poisoning (3.39, 1.74 to 6.60), suicide (4.32, 1.85 to 10.08), respiratory disease (3.72, 1.54 to 9.00), and diseases of the digestive system (3.30, 1.08 to 10.09; table S5). As with total mortality, most associations were substantially unchanged when we additionally adjusted for adult covariates (table 2, table 3, and table S5). We did not find any evidence of associations for cancer mortality.

We found multiplicative ($P=0.01$) and additive ($P=0.004$) interactions between physical and sexual abuse on the risk of total premature mortality (table S6), in which those with severe abuse of both types were at the highest risk of premature mortality. Meanwhile, although there was no evidence of either multiplicative

or additive interaction between physical abuse and social support, we found positive interaction on the additive scale between sexual abuse and social support on the risk of premature mortality ($RERI=0.17$, 95% confidence interval -0.02 to 0.36 ; $P=0.08$). We did not find any evidence of interaction between early life abuse and adult diet quality, body mass index, physical activity, and depression on the risk of total premature mortality (table 4). However, the association of sexual abuse with total premature mortality was stronger among nurses who smoked or had a higher anxiety score during adulthood ($RERI=0.63$, 0.28 to 0.98 ; and 0.54 , 0.19 to 0.89 , respectively). Mediation analyses showed that smoking, low levels of physical activity, anxiety, and depression explained 12.9% (95% confidence interval 9.1% to 18.0%), 3.9% (2.7% to 5.7%), 4.7% (2.8% to 7.7%), and 20.7% (14.4% to 28.9%) of the association between physical abuse and premature mortality, respectively (table 4). A similar mediated proportion was observed for the association between sexual abuse and premature mortality (16.2%, 10.8% to 23.5%; 7.3%, 4.9% to 10.9%; 5.9%, 3.5% to 9.9%; and 22.4%, 14.7% to 32.7%, respectively). We found that neither obesity nor diet mediated the associations of early life abuse with premature mortality.

The positive associations between early life physical and sexual abuse and total mortality persisted after excluding nurses reporting a diagnosis of cardiovascular disease or cancer in 2001, redefining premature death as those who died before age 65 years, including deaths at or after 70 years of age, and adjusting for more refined smoking covariates (smoking status, pack years of smoking, and the square of pack years) or the presence of another early life abuse (physical or sexual abuse; table S7).

Discussion

Principal findings

In this large prospective study with 18 years of follow-up, we found an increased risk of premature adult mortality in female nurses reporting moderate to severe physical abuse and forced sexual activity before age 12 and at ages 12-17 years. When the most common causes of premature mortality were considered, severe physical abuse was associated with a greater risk of mortality due to external causes of injury and poisoning, suicide, and diseases of the digestive system, while severe sexual abuse was associated with a greater risk of mortality due to cardiovascular diseases, external causes of injury and poisoning, suicide, respiratory disease, and diseases of the digestive system.

Comparison with previous studies

In support of our results, previous studies reported that adverse childhood experiences, of which physical and sexual abuse constitute only a part of six to eight domain adverse childhood experience measures, were associated with a greater risk of all cause mortality.^{17 51 52} Early life maltreatment, a combined measure of abuse and neglect, has also been

associated with a greater risk of total or injury related mortality during adulthood.¹⁶⁻¹⁹ In a large retrospective cohort study of 331 254 young Australians, Segal and colleagues reported a greater risk of total and cause specific mortality (eg, deaths from suicide, poisonings, or alcohol) between ages 16 and 33 years among those with versus those without child protection service involvement.²¹ However, few population studies to date have explored the association of individual types of early life abuse with subsequent long term risk of mortality. In a national sample of 3298 US women, Chen and colleagues reported a greater risk of total mortality over two decades of follow-up among women reporting childhood physical abuse (hazard ratio 1.30, 95% confidence interval 1.05 to 1.60 for moderate physical abuse; and 1.58, 1.20 to 2.08 for severe physical abuse) or emotional abuse (1.22, 1.01 to 1.49) compared with those without such an experience; they did not evaluate sexual abuse.²² Similarly, in a British prospective cohort study consisting of 9310 adults, Rogers and colleagues revealed a greater risk of total mortality at ages 44-58 years among adults reporting childhood sexual (hazard ratio 2.64, 95% confidence interval 1.52 to 4.59) or physical abuse (1.73, 1.11 to 2.71) than those without such abuse.²⁰

Our study extends and refines the existing evidence in this area. We included a larger population with detailed information on causes of death and abuse history, which permitted us to separately examine the risk for cause specific mortality in relation to physical and sexual abuse. We found that both early life sexual and physical abuse were associated with a greater risk of mortality. Specifically, severe physical and forced sexual activity in childhood or adolescence were both associated with a greater risk of mortality due to external causes (injury and poisoning), suicide, and diseases of the digestive system. Additionally, we found that forced sexual activity, especially if it occurred in childhood and adolescence, was associated with a greater risk of mortality due to cardiovascular disease and respiratory disease. In support of our findings, early life physical or sexual abuse has been associated with an increased risk of suicide attempts,^{53 54} cardiovascular diseases,^{11 14} respiratory diseases,⁵⁵ and gastrointestinal illnesses in later life,⁵⁶ which might eventually lead to a greater risk of mortality. Similarly, in a meta-analysis consisting of 37 studies, Hughes and colleagues estimated the risk for 23 outcomes and found that adverse childhood experiences were associated with a greater risk of suicide attempt, illicit or problematic drug use, cardiovascular diseases (eg, heart attack, coronary heart disease, or ischemic heart disease), chronic respiratory diseases (eg, tuberculosis and chronic obstructive pulmonary disease), and digestive diseases (liver disease, jaundice, or hepatitis).⁵⁷ Several studies showed positive associations between the number of adverse childhood experiences and cancer incidence,^{58 59} but no study has explored the associations of early life abuse with cancer mortality. In the present study, neither physical nor sexual abuse was associated with cancer mortality. We suspect that many nurses

who develop cancer might still have not died due to advances in medical treatment. However, given the limited sample size for some cause specific mortality categories, additional studies are needed to verify our findings.

We also observe evidence of interaction between sexual and physical abuse; the risk of premature mortality was particularly strong among participants who experienced both severe physical abuse and forced sexual activity. Additionally, we found that the association of sexual abuse with premature mortality was stronger among female nurses who smoked and had higher anxiety scores during later adulthood, suggesting that early life sexual abuse could interact synergistically with adult smoking and anxiety disorders to further increase the risk of premature mortality. However, it is somewhat surprising that obesity was not a mediator of the associations of child abuse with adult mortality, given higher rates of obesity among those with a history of child abuse,^{25 60} the adverse effect of obesity on premature mortality,⁶¹ and higher rates of adult obesity in those with severe physical or sexual abuse in the present study. It should be noted that the association of childhood or adolescent physical and sexual abuse with premature mortality observed in the present study was mainly driven by mortality due to external causes and suicide that were less likely to be influenced by obesity. Meanwhile, we found evidence of positive interaction on the additive scale between sexual abuse and social support on the risk of premature mortality, suggesting that the association of sexual abuse with premature mortality is greater among female nurses receiving rare or no social support. Our findings were supported by a recent study of 6078 US adults showing that midlife social support could offset mortality risk associated with early life abuse.⁶²

Possible underlying mechanisms

One explanation underlying the associations of early life abuse with premature mortality due to chronic diseases (cardiovascular disease, respiratory disease, and diseases of the digestive system), injuries, and suicides is that abuse might heighten vulnerability to mental health problems and adverse lifestyle patterns.¹⁴ In support of this hypothesis, our study shows that part of the associations between physical and sexual abuse and premature mortality was mediated by smoking, low levels of physical activity, anxiety, and depression during adulthood. Numerous studies have documented associations between early life maltreatment and abuse and subsequent risk of psychological disorders and emotional distress, including depression.^{15 63 64} Early life abuse has also been associated with an increased risk of unhealthy behaviors, such as smoking and alcohol consumption.^{24 65 66} These psychological and behavioral problems, in turn, might heighten the risk for later life morbidity or mortality of cardiovascular disease, injury, suicide, respiratory disease, and diseases of the digestive system. Other

potential mechanisms are related to biological changes across body systems, including immune and inflammatory function, brain development trajectories, and neuroendocrine stress activities.¹³ For instance, previous studies from other populations or subsamples of NHSII participants have shown that childhood or adolescent abuse is associated with higher concentrations of inflammatory biomarkers (eg, C reactive protein, interleukin 1 β , and interleukin 6),^{67 68} altered brain structure, function, and network architecture,¹⁵ impaired cellular immunity,⁶⁹ and dysregulated neuroendocrine stress system.^{13 70} Early life abuse and other stressful life experiences have also been associated with epigenetic modifications,⁷¹ which could alter the trajectories of brain development, eventually leading to psychiatric disorders and addictive behaviors in adulthood.^{72 73} Interestingly, the increased risk of mortality due to cardiovascular disease and respiratory disease was only observed among female nurses reporting forced sexual activity, rather than physical abuse. Given that smoking, physical activity, anxiety, and depression consistently mediated a greater proportion of the associations for forced sexual activity than physical abuse, we suspected that those who experienced sexual violence were more likely to be influenced by subsequent mental disorders and adverse lifestyle patterns, which themselves have been positively associated with cardiovascular diseases and respiratory diseases.^{74 75}

Strengths and limitations

The strengths of this study include its large sample size, prospective follow-up over 18 years with excellent response rates, detailed information on causes of death and abuse history, and the collection of various relevant confounders, psychosocial outcomes (eg, depression), and lifestyle factors (eg, smoking). Our study also has some limitations. Participants recalled their childhood and adolescent abuse in 2001 when they were aged 37–54 years, which might have resulted in recall bias and exposure misclassification. However, we queried specific acts of early life abuse instead of asking participants to characterize their experience as abuse, which should create less bias.^{11 76} As a result, our cumulative prevalence of moderate to severe physical abuse was within the range of the prevalence of severe parental violence in the UK, the US, New Zealand, Finland, Italy, and Portugal (5–35% v 34.9%, 23 659 of 67 726 in NHSII).⁴ Similarly, the cumulative prevalence of any (15–30%) and penetrative sexual abuse (5–10%) in developed countries (US, Australia, New Zealand, and Canada) was also comparable to the prevalence in NHSII (33.5%, 22 718 of 67 726; and 11.3%, 7673 of 67 726, respectively).⁴ The slightly higher overall prevalence of physical and sexual abuse in NHSII is probably reflective of the dramatic decline in childhood abuse rate over the past several decades in the US.⁷⁷ Meanwhile, several previous studies have shown that adults' recall of early life abuse is reliable.^{78 79} However, problems such as forgetting, denial, misunderstanding, and embarrassment are

still likely to lead to an underestimated report of early life abuse.⁴ In this case, since childhood or adolescent abuse was reported before premature mortality, we suspected that the underestimated abuse would be non-differential with respect to adult mortality and that our findings were unlikely to be included by exposure misclassification.

Selection bias cannot be fully excluded given that those who experienced abuse might have refused to return the violence questionnaire. However, we found a similar pattern of age standardized characteristics between included female nurses and those excluded due to missing exposure information in 2001. The NHSII cohort includes primarily non-Hispanic white female nurses. Therefore, our results should be interpreted with caution to the general female population and other more diverse populations who might have different educational attainment, socioeconomic status, social support resources, and risk factors for premature mortality. As with any other observational study, our study cannot show causality. Because randomizing women to experience abuse is impossible, high quality observational studies with extended follow-up are likely to provide the best available evidence to assess the long term effects of early life abuse. It is also likely there are factors (eg, social and structural factors) associated with childhood abuse that could affect early mortality and thus confound the associations we identified.⁸⁰

⁸¹ However, our findings were materially unchanged across the adjustments for socioeconomic status (parental education, home ownership, job types), birthplaces, and time varying adult characteristics, and were robust to a series of sensitivity analyses. We did not collect data on psychological aids or therapies and other adverse childhood experiences (eg, household violence and substance abuse) and adult psychiatric disorders (eg, schizophrenia, substance use disorders, and bipolar disorder) that could also play an interactive or mediating role. Finally, we have limited numbers for some categories of death, such as respiratory diseases and diseases of the digestive track, which limited our ability to generate precise estimates for some causes of death. Additional studies with larger numbers of deaths are needed to verify our findings for cause specific deaths.

Conclusion and policy implications

This large prospective study consisting of 67 726 female nurses showed that moderate to severe physical abuse and forced sexual activity in early life were associated with a greater subsequent risk of total premature mortality. These associations were driven by various reasons for death, including external causes, suicide, cardiovascular disease, respiratory disease, and diseases of the gastrointestinal system, and could be partly mediated by later life smoking, low levels of physical activity, anxiety, and depression. Together, these findings suggest that women who experienced childhood physical and sexual abuse continue to be vulnerable to premature mortality and highlight

that efforts to prevent child abuse might have long reaching benefits for population health and longevity by reducing premature mortality. Additionally, we found evidence of an interactive or mediating role of social support, psychological conditions, and lifestyle factors, which emphasizes the importance of social supporting services and psychological or lifestyle interventions in improving health outcomes for those who have experienced child abuse.

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Contributors: Y-XW analyzed and drafted the manuscript. YS checked the accuracy of the data analysis. Y-XW, JEC, and JWR-E were involved in the study conception and design. All authors participated in the interpretation of the results and critical revision of the manuscript. JWR-E is the study guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the National Institutes of Health for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and the Harvard TH Chan School of Public Health (protocol No: 2009-P-002375). The completion of the self-administered questionnaire was considered to imply informed consent.

Data sharing: Data described in the manuscript, code book, and analytic code will not be made publicly available. Further information including the procedures for obtaining and accessing data from the Nurses' Health Studies II is described at <https://www.nurseshealthstudy.org/researchers> (email: nhsaccess@channing.harvard.edu).

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Study participants are periodically updated on findings from the study through multiple channels including our yearly newsletter, the study website, and our social media feeds.

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Web appendix: Supplemental material