Intake of fruits and vegetables according to pesticide residue status in relation to all-cause and disease-specific mortality: Results from three prospective cohort studies

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ABSTRACT

Background: Intake of conventionally grown fruits and vegetables (FVs) is an important route of exposure to pesticide residues in the general population. However, whether health risk stemming from exposure to pesticides through diet could offset benefits of consuming FVs is unclear.

Objective: We assessed the association of FV intake, classified according to their pesticide residue status, with total and cause-specific mortality.

Methods: We followed 137,378 women (NHS, 1998–2019, and NHSII, 1999–2019) and 23,502 men (HPFS, 1998–2020) without cardiovascular disease, cancer, or diabetes at baseline. FV intake was assessed using validated food frequency questionnaires and categorized as having high- or low-pesticide-residues using data from the USDA Pesticide Data Program. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for total and cause-specific mortality associated with high- and low-pesticide-residue FV intake.

Results: A total of 27,026 deaths, including 4,318 from CVD and 6,426 from cancer, were documented during 3,081,360 person-years of follow-up. In multivariable-adjusted analyses, participants who consumed ≥4 servings/day of low-pesticide-residue FVs had 36% (95% CI: 32%-41%) lower mortality risk compared to participants who consumed <1 serving/day. The corresponding estimate for high-pesticide residue FV intake was 0.93 (95% CI: 0.81–1.07). This pattern was similar across the three most frequent causes of death (cardiovascular disease, cancer and respiratory diseases).

Conclusions: High-pesticide-residue FV intake was unrelated whereas low-pesticide residue FV intake was inversely related to all-cause mortality, suggesting that exposure to pesticide residues through diet may offset the beneficial effect of FV intake on mortality.

1. Introduction

Fruit and vegetables (FVs) are considered an integral part of a healthy diet and thus recommended by major organizations and government guidelines across the world; mostly for their well-documented benefits in the prevention of cardiovascular disease (CVD) (Millen et al.,

2016; Eckel et al., 2014). Nevertheless, the main exposure route for pesticide residues in the general population is diet, (Xue et al., 2014; Yu et al., 2012; Fortes et al., 2013; Lu et al., 2008) particularly through the consumption of conventionally grown FVs. Data from the USDA Pesticide Data Program (PDP), which systematically surveys the presence of pesticide residues in foods sold in supermarkets, shows that in 2018

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more than 50% of FVs consumed in the U.S. contained detectable pesticide residues and more than 30% had two or more pesticides (Ams, 2018).

Occupational exposure to pesticides used in agriculture is known to increase morbidity and mortality (Suratman et al., 2015). In fact, several pesticides have been banned in the last 50 years, but they can still persist on water and soil (Jones and de Voogt, 1999; Lovecka et al., 2015; Pouch et al., 2018). Moreover, risk assessments by the International Agency for Research on Cancer (IARC) have concluded that occupational exposure to certain pesticides used in agriculture is carcinogenic to humans. (IARC, 1991) Although tolerance levels of pesticides are regulated by the Environmental Protection Agency (EPA), these do not necessarily imply lack of adverse health effects in humans and therefore long-term deleterious effects on human health of pesticide residues through diet remain unclear. We have previously reported that exposure to pesticide residues through FV intake may reduce the benefits of FV intake on CVD incidence (Chiu et al., 2019) and is associated with adverse reproductive outcomes. (Chiu et al., 2018; Chiu et al., 2015) Others have reported benefits of consuming organic produce on cancer risk, (Baudry et al., 2018) whereas overall exposure to pesticides through FV intake was not associated with cancer risk. (Sandoval-Insausti et al., 2021) However, it is not clear whether these apparent benefits on the incidence of major chronic non-communicable diseases can impact mortality. To address this question, we examined the association of FV intake, considering their pesticide residue status based on surveillance data, with total and cause-specific mortality in three cohorts of U.S. health professionals.

2. Methods

2.1. Study population

We included participants from three ongoing U.S. based prospective cohorts: the Nurses' Health Study (NHS) which included 121,700 female registered nurses aged 30–55 years in 1976; the Nurses' Health Study II (NHSII) which included 116, 671 female registered nurses, aged 25–42 in 1989; and the Health Professionals Follow-up Study (HPFS) which included 51,529 male health professionals aged 40–75 in 1986. (Bao et al., 2016) At baseline and biennially thereafter, participants of all cohorts were asked to complete a self-administered questionnaire to obtain information on demographic factors, lifestyle, and medical history. Habitual food consumption was recorded every four years using an extensively validated food frequency questionnaire (FFQ) with 131 food items, of which 27 were fruits and vegetables. (Rimm et al., 1992; Yuan et al., 20182018; Yuan et al., 2017) The follow-up rates in each cycle were around 90%. In the current analysis, we followed individuals from 1998 (in NHS and HPFS) and 1999 (in NHSII) based on the ability to couple information on FV intake from prospectively collected FFQs with contemporaneous national surveillance data on pesticide residues in food. We excluded participants with cardiovascular disease, cancer, or diabetes at baseline. We also excluded participants with missing or invalid total energy intakes (<500 or greater than 3500 kcal/day for women and < 800 or greater than 4200 kcal/day for men) or who lacked data on more than 50% of the FVs related questions. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required.

2.2. Pesticide residue assessment

FVs reported in the FFQ were classified as having high- or low-pesticide-residues using the Pesticide Residue Burden Score (PRBS), a validated score system used to ascertain pesticide residues in FVs. (Hu et al., 2016; Chiu et al., 2018) Briefly, we linked period-matched data on pesticide residues in FVs as reported in surveillance data from the PDP, (Ams, 2018) with individual level FV intake data as reported in the FFQ. PDP database includes approximately 420 pesticides and their

metabolites. In 2018, detectable levels of at least one pesticide was reported in more than 50% of conventionally grown FVs in and 2 or more pesticides were detected in 31% of the fruits and vegetables analyzed. (Ams, 2018) PDP data from 1996 to 1999 was paired to FFQ data from 1998 (NHS/HPFS) and 1999 (NHSII); PDP data from 2000 to 2003 was paired to FFQ data from 2002 and 2003; until 2012–2013. Each FV included in the FFQ was ranked according to three measures obtained from the PDP: 1) the percentage of samples with any detectable pesticide residues; 2) the percentage of samples with any pesticide residues above tolerance levels; and 3) the percentage of samples with three or more individual detectable pesticides. For each contamination measure, a score of 0 was assigned for FVs in the lowest tertile, 1 for FVs in the middle tertile, and 2 for FVs in the highest period-specific tertile. The PRBS was the sum of scores across the three measures on a scale of 0 to 6. Then, for each period, FVs with PRBS $\geq$ 4 were classified as having high-pesticide-residue status, FVs with PRBS < 4 as having low-pesticide-residue status, and FVs without matching PDP data as having undetermined -pesticide residue status. Finally, intakes of high-, low-, and undetermined pesticide-residue FVs were summed for each participant in the three cohorts (Table S1). (Chiu et al., 2019)

2.3. Covariates

In the questionnaires, participants self-reported diagnoses of hypertension, hypercholesterolemia, cardiovascular disease, cancer, and diabetes as well as information on race, body mass index (BMI), physical activity, family history of cancer and cardiovascular disease, smoking status, and smoking in package-years. Further information on total energy intake, alcohol intake, and the Alternate Healthy Eating Index, excluding criteria for intake of FVs and alcohol, was collected every four years. (McCullough and Willett, 2006; Chiuve et al., 2012) In the NHS and NHSII, updated data on postmenopausal status and current hormone therapy use were also gathered.

2.4. Outcome assessment

Our main outcome was all-cause mortality. Deaths from the three cohorts were assessed from state vital records, National Death Index, and reports from family members or the postal authorities. These methods ascertained more than 98% of the deaths. (Rich-Edwards et al., 1994) The cause of death was classified according to the International Classification of Diseases, Eighth Revision (ICD-8) in four categories: deaths from cardiovascular disease (heart failure, coronary heart disease, stroke, and any other vascular disease; ICD codes: 390–458), deaths from cancer (ICD codes: 140–207), deaths from respiratory diseases (ICD codes: 460–519), and other causes of death (Table S2). We also calculated premature deaths, defined as deaths before age 70 years, in all the three cohorts. (Shiels et al., 2017)

2.5. Statistical analysis

We followed the participants from the date of the return of the baseline questionnaire to the date of death or the end of follow up (June 2019 in NHS and NHSII and June 2020 in HPFS), whichever occurred first. Cumulative average intakes of high- and low-pesticide-residue FVs over updated questionnaires were calculated and modeled in categories of absolute intake (<1, 1–1.9, 2–2.9, 3–3.9, $\geq$4 servings/day) and as quintiles of intake. The associations between high- and low-pesticide-residue FV intake and all-cause, cause-specific, and premature mortality were summarized with Hazard Ratios (HRs) and their 95% confidence interval (95% CI) obtained from Cox proportional hazards regression models with age as the time scale. In the multivariable analysis, we adjusted for age (years), BMI (quintiles), race (white/nonwhite), physical activity (quintiles), family history of cancer (yes/no), family history of cardiovascular disease (yes/no), smoking in package-years (never smoker, 1–4.9, 5–19.9, 20–39.9, or greater than 40),

baseline hypertension (yes/no), baseline hypercholesterolemia (yes/no), total energy intake (quintiles), alcohol intake (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, or greater than 30 g/day), and a modified version of the Alternate Healthy Eating Index (quintiles), which excluded scoring for intakes of fruits, vegetables, and alcohol. In the NHS and NHSII, we further adjusted for postmenopausal hormone use (premenopausal/

never/past/current). For intakes of high-pesticide-residue FVs, the multivariable model was additionally adjusted for intakes of low-pesticide-residue FVs and other FVs with undetermined-pesticide-residues. Similarly, models for low-pesticide-residue FV intake were further adjusted for intakes of high-pesticide-residue FVs and other FVs with undetermined- pesticide-residue status. Tests for linear trend were

Table 1
Baseline characteristics of participants according to absolute intakes of high- and low-pesticide-residue fruits and vegetables.

Characteristics	High-Pesticide-Residue Fruit and Vegetable Intake (servings/day)			Low-Pesticide-Residue Fruit and Vegetable Intake (servings/day)		
	<1	≥2-< 3	≥4	<1	≥2-< 3	≥4
Nurses' Health Study (1998)						
Number of participants	20,267	10,096	1,512	7,821	17,717	4,626
High-pesticide-residue FVs (servings/day)	0.6(0.2)	2.4(0.3)	5.2(1.4)	0.8(0.7)	1.7(0.9)	2.6(1.4)
Low-pesticide-residue FVs (servings/day)	1.6(0.9)	2.8(1.2)	3.8(1.9)	0.7(0.2)	2.4(0.3)	5.0(1.3)
Total FVs (servings/day)	2.9(1.2)	6.4(1.5)	10.7(2.9)	2.2(1.0)	5.1(1.3)	9.0(2.5)
Age (y)	63.6(7.2)	64.0(6.9)	62.8(6.5)	64.0(7.3)	63.8(7.0)	63.5(6.7)
BMI (kg/m^2)	26.6(5.3)	26.1(4.9)	25.4(4.9)	26.5(5.2)	26.3(5.0)	26.0(4.9)
Postmenopause (%)	93.4	93.3	94.1	93.2	93.2	93.6
White (%)	97.7	97.7	96.9	97.1	97.9	96.8
Physical activity (MET/wk)	13.2(17.9)	22.8(24.7)	30.4(30.6)	13.0(18.1)	18.9(21.9)	25.1(27.5)
Family history of cancer (%)	21.5	23.0	23.7	21.0	22.2	22.7
Family history of cardiovascular disease (%)	6.6	7.0	6.8	6.8	6.4	6.7
Never smoker (%)	43.5	50.1	48.6	42.0	48.0	51.0
No of pack-years among ever smokers	15.9 (21.8)	9.9(16.3)	9.7 (15.5)	17.3(22.7)	11.6(18.0)	10.4(17.2)
Current hormone therapy use (%)	45.9	49.4	48.1	44.5	48.7	48.3
Hypertension (%)	39.6	38.1	35.3	37.3	38.9	41.7
Hypercholesterolemia (%)	54.7	53.3	50.2	54.1	53.8	53.5
Total energy intake (kcal/day)	1,527(482)	1,932(521)	2,166(568)	1,373(452)	1,807(477)	2,227(538)
Alcohol intake (g/day)	5.2(9.7)	5.1(8.4)	4.5(7.7)	4.5(9.4)	5.5(9.2)	5.5(9.2)
Modified AHEI (score)*	38.1(8.3)	40.4(8.5)	41.9(8.8)	41.4(8.6)	38.2(8.3)	37.9(8.0)
Nurses' Health Study II (1999)						
Number of participants	33,222	10,669	1,921	13,978	20,124	4,939
High-pesticide-residue FVs (servings/day)	0.6(0.3)	2.4(0.4)	5.4(1.6)	0.7(0.6)	1.6(0.9)	2.6(1.6)
Low-pesticide-residue FVs (servings/day)	1.5(0.9)	2.8(1.2)	3.8(2.1)	0.7(0.2)	2.4(0.3)	5.1(1.3)
Total FVs (servings/day)	2.5(1.2)	6.1(1.6)	10.5(3.4)	1.8(0.9)	4.8(1.3)	8.9(2.9)
Age (y)	44.4(4.7)	45.0(4.6)	45.1(4.6)	44.5(4.7)	44.7(4.6)	45.0(4.6)
BMI (kg/m^2)	26.7(6.3)	25.9(5.7)	25.4(5.7)	26.9(6.4)	26.1(5.9)	26.0(6.0)
Postmenopause (%)	22.2	22.0	21.7	23.1	21.3	21.8
White (%)	96.2	97.1	95.4	95.4	97.2	95.1
Physical activity (MET/wk)	14.7(19.2)	23.3(24.3)	29.8(31.2)	14.3(19.4)	19.9(22.7)	26.0(30.0)
Family history of cancer (%)	19.3	20.0	21.9	19.4	19.8	19.5
Family history of cardiovascular disease (%)	33.9	32.8	33.1	33.9	32.7	33.1
Never smoker (%)	65.3	67.1	64.7	64.1	67.3	68.7
No of pack-years among ever smokers	5.2(9.8)	3.8(7.5)	4.1(7.6)	5.7(10.4)	4.0(8.0)	3.7(7.6)
Current hormone therapy use (%)	1.0	1.2	1.1	1.1	0.9	1.1
Hypertension (%)	13.2	12.5	11.1	13.2	12.8	13.3
Hypercholesterolemia (%)	25.6	22.8	22.9	24.9	23.8	22.7
Total energy intake (kcal/day)	1,632(521)	2,086(542)	2,270(578)	1,458(475)	1,959(509)	2,375(542)
Alcohol intake (g/day)	3.7(9.1)	4.2(6.8)	3.9(7.2)	3.2(7.2)	4.3(7.1)	4.3(7.5)
Modified AHEI (score)*	37.4(9.1)	40.2(9.7)	42.9(10.0)	39.9(9.2)	37.8(9.4)	37.7(9.3)
Health Professionals Follow-up Study (1998)						
Number of participants	7,763	4,106	845	2,394	7,219	2,576
High-pesticide-residue FVs (servings/day)	0.6(0.2)	2.4(0.3)	5.4(1.5)	0.9(0.7)	1.6(0.9)	2.6(1.6)
Low-pesticide-residue FVs (servings/day)	1.8(1.0)	3.0(1.3)	4.0(2.0)	0.7(0.2)	2.5(0.3)	5.2(1.3)
Total FVs (servings/day)	3.1(1.3)	6.6(1.6)	11.2(2.9)	2.2(1.0)	5.1(1.3)	9.2(2.7)
Age (y)	62.1(8.5)	64.3(8.7)	64.5(8.9)	62.2(8.5)	63.4(8.7)	63.2(8.7)
BMI (kg/m^2)	26.2(3.4)	25.6(3.4)	25.5(3.5)	26.3(3.5)	25.9(3.4)	25.8(3.6)
White (%)	90.4	91.6	92.5	90.1	91.7	90.6
Physical activity (MET/wk)	28.3(33.5)	43.7(44.2)	54.6(51.4)	26.9(35.8)	36.6(38.8)	48.0(48.5)
Family history of cancer (%)	9.8	10.7	12.0	8.6	11.0	10.1
Family history of cardiovascular disease (%)	9.5	9.6	9.4	9.8	10.2	8.6
Never smoker (%)	50.8	57.7	62.6	50.4	55.6	61.1
No of pack-years among ever smokers	13.3(19.2)	8.7(14.3)	7.7(12.7)	13.7(19.3)	10.2(16.0)	8.5(14.8)
Hypertension (%)	33.0	29.6	28.7	31.1	31.0	32.1
Hypercholesterolemia (%)	45.5	42.5	41.6	45.1	43.5	41.0
Total energy intake (kcal/day)	1,797(558)	2,198(610)	2,484(646)	1,607(513)	2,046(562)	2,490(643)
Alcohol intake (g/day)	12.0(15.7)	10.5(12.8)	9.3(11.8)	11.0(15.7)	11.5(14.0)	10.5(12.9)
Modified AHEI (Score)*	32.3(8.0)	37.0(8.0)	40.3(8.7)	34.8(8.9)	34.4(8.1)	35.8(8.0)

Values are means (SD) or percentages. All variables except age are age-standardized.
Abbreviations: Modified AHEI, Modified Alternate Healthy Eating Index score; BMI, body mass index; METs: metabolic equivalent tasks; FV: fruits and vegetables.
*Modified AHEI: AHEI-2010, but excluding criteria for intakes of fruits and vegetables and alcohol.
METs are defined as the ratio of caloric needed per kilogram of body weight per hour of physical activity divided by the caloric needed per kilogram of body weight at rest.

assessed by modeling as a continuous variable the median values of each category of consumption. Analyses were carried out separately for each cohort and then were pooled using a fixed-effect model. To test for non-linear associations and examine the dose–response relationships, we depicted restricted cubic splines with four knots using the exposure variables as continuous in fully-adjusted models. Finally, we estimated the effect of substituting high-pesticide-residue FVs with low-pesticide-residue FVs by modeling both as continuous variables in the same model and using the difference of the regression coefficients as the point estimate, and the covariance matrix to estimate 95 %CIs. We also carried out cohort-specific analyses and evaluated the intake of FVs modeled as quintiles, the deaths before age 70 years, and the most recent diet

assessment. Moreover, we did not see evidence of effect modification by various established risk factors for premature mortality.

Analyses were performed with SAS software version 9.4 for UNIX (SAS Institute, Cary, NC), at a two sided p<0.05.

3. Results

We identified 27,026 deaths over 3,081,360 person-years of follow-up, including 4,318 from CVD, 6,426 from cancer, 2,012 from respiratory diseases, and 14,222 from other causes. Of these deaths, 3,492 took place before age 70 years. Participants who consumed ≥ 4 servings/day of high-pesticide-residue FV intake were more frequently active, never

Table 2

Pooled hazard ratios (95% CI) of total mortality, CVD mortality, cancer mortality, respiratory mortality, and other causes of death according to absolute intakes of high- and low-pesticide-residue fruits and vegetables in the NHS, NHSII, and HPFS.

	High-Pesticide-Residue Fruit and Vegetable Intake (servings/day)					P, trend
	<1	≥1-<2	≥2-<3	≥3-<4	≥4	
Total mortality (n = 27,026)						
Person-years	1,228,473	1,280,067	426,074	102,468	44,278	
Cases	12,133	10,777	3,185	696	235	
Age-adjusted	1 (Ref.)	0.70 (0.68, 0.72)	0.62(0.60, 0.65)	0.63(0.59, 0.69)	0.59(0.52, 0.68)	<0.0001
Multivariable-adjusted[1,2]	1 (Ref.)	0.95 (0.92, 0.99)	0.97(0.92, 1.02)	1.01(0.93, 1.11)	0.93(0.81, 1.07)	0.84
CVD mortality (n = 4,318)						
Cases	1,861	1,764	539	113	41	
Age-adjusted[1]	1 (Ref.)	0.74(0.70, 0.80)	0.64(0.58, 0.71)	0.61(0.50, 0.75)	0.56(0.41, 0.78)	<0.0001
Multivariable-adjusted[1,2] 1 (Ref.) 1.03 (0.95, 1.12) 1.00 (0.88, 1.14) 1.03(0.82, 1.28) 0.95(0.67, 1.34) 0.76						
Cancer mortality (n = 6,426)						
Cases	2,722	2,583	854	198	69	
Age-adjusted	1 (Ref.)	0.76(0.72, 0.81)	0.72(0.67, 0.78)	0.72(0.62, 0.83)	0.67(0.53, 0.85)	<0.0001
Multivariable-adjusted[1,2]	1 (Ref.)	0.93(0.87, 1.00)	1.01(0.92, 1.12)	1.02(0.86, 1.20)	0.93(0.72, 1.20)	0.95
Respiratory mortality (n = 2,012)[4]						
Cases	1,009	730	212	48	13	
Age-adjusted	1 (Ref.)	0.56 (0.51, 0.61)	0.47 (0.40, 0.55)	0.51(0.38, 0.68)	0.38(0.22, 0.66)	<0.0001
Multivariable-adjusted[1,2]	1 (Ref.)	0.85 (0.75, 0.96)	0.90 (0.74, 1.09)	1.05(0.76, 1.47)	0.66(0.36, 1.19)	0.41
Other causes of death (n = 14,222)[5]						
Cases	6,516	5,682	1,575	337	112	
Age-adjusted	1 (Ref.)	0.69(0.66, 0.71)	0.59(0.56, 0.63)	0.63(0.56, 0.70)	0.63(0.52, 0.76)	<0.0001
Multivariable-adjusted[1,2]	1 (Ref.)	0.96(0.92, 1.00)	0.94(0.88, 1.02)	1.10(0.97, 1.25)	1.17(1.09, 1.25)	0.78
	Low-Pesticide-Residue Fruit and Vegetable Intake (servings/day)					**P, trend**
	<1	≥1-<2	≥2-<3	≥3-<4	≥4	
Total mortality (n = 27,026)						
Person-years	398,732	956,163	950,927	501,456	274,083	
Cases	3,808	8,324	8,230	4,296	2,368	
Age-adjusted	1 (Ref.)	0.67 (0.65, 0.70)	0.54 (0.52, 0.56)	0.48 (0.46, 0.50)	0.47 (0.44, 0.49)	<0.0001
Multivariable-adjusted[1,3]	1 (Ref.)	0.81 (0.77, 0.84)	0.72 (0.68, 0.75)	0.65 (0.62, 0.69)	0.64 (0.59, 0.68)	<0.0001
CVD mortality (n = 4,318)						
Cases	611	1,279	1,258	725	445	
Age-adjusted	1 (Ref.)	0.66 (0.60, 0.73)	0.51 (0.46, 0.57)	0.48 (0.43, 0.54)	0.49 (0.43, 0.56)	<0.0001
Multivariable-adjusted[1,3]	1 (Ref.)	0.77 (0.69, 0.86)	0.65 (0.57, 0.73)	0.64 (0.55, 0.74)	0.70 (0.58, 0.83)	<0.0001
Cancer mortality (n = 6,426)						
Cases	762	1,989	2,053	1,071	551	
Age-adjusted	1 (Ref.)	0.82(0.76, 0.90)	0.72(0.66, 0.78)	0.65(0.59, 0.72)	0.60(0.54, 0.67)	<0.0001
Multivariable-adjusted[1,3]	1 (Ref.)	0.95(0.86, 1.04)	0.91(0.82, 1.01)	0.87(0.77, 0.98)	0.81(0.69, 0.94)	<0.01
Respiratory mortality (n = 2,012)[4]						
Cases	317	640	589	306	160	
Age-adjusted	1 (Ref.)	0.62 (0.54, 0.71)	0.46 (0.40, 0.53)	0.39 (0.33, 0.46)	0.36 (0.29, 0.44)	<0.0001
Multivariable-adjusted[1,3]	1 (Ref.)	0.80 (0.69, 0.93)	0.71 (0.59, 0.84)	0.65 (0.52, 0.80)	0.62 (0.47, 0.82)	<0.0001
Other causes of death (n = 14,222)[5]						
Cases	2,107	4,396	4,319	2,190	1,210	
Age-adjusted	1 (Ref.)	0.63(0.60, 0.67)	0.50(0.47, 0.52)	0.43(0.40, 0.45)	0.43(0.40, 0.46)	<0.0001
Multivariable-adjusted[1,3]	1 (Ref.)	0.77(0.73, 0.81)	0.67(0.62, 0.72)	0.60(0.55, 0.65)	0.56(0.51, 0.63)	<0.0001

Abbreviations: NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; HPFS, Health Professionals Follow-up Study.

[1] Adjusted for age, body mass index (quintiles), ethnicity (white/non-white), physical activity (quintiles), family history of cancer (yes/no), family history of cardiovascular disease (yes/no), smoking in package-years (never smoker, 1–4.9, 5–19.9, 20–39.9, or ≥ 40), postmenopausal hormone use (premenopausal/never/past/current, in NHS and NHSII), baseline hypertension (yes/no), baseline hypercholesterolemia (yes/no), total energy intake (quintiles), alcohol intake (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, or ≥ 30 g/day), and Alternate Healthy Eating Index score excluding criteria for intake of fruits and vegetables and alcohol (quintiles).

[2] Additionally adjusted for intakes of low-pesticide-residue fruits and vegetables (servings/day) and other fruits and vegetables with undetermined residues (quintile).

[3] Additionally adjusted for intakes of high-pesticide-residue fruits and vegetables (servings/day) and other fruits and vegetables with undetermined residues (quintile).

[4] Respiratory mortality only included NHS and HPFS.

[5] Other causes of death included diabetes, neurological disease, kidney diseases, injury or poison, suicide, and all other causes.

smokers and were more likely to have hypercholesterolemia, had a lower BMI, and a higher consumption of total calories, total FVs, flavonoids, antioxidant nutrients, and fiber. (Table 1 and Table S3). We observed the same pattern of association between baseline characteristics and intake of low-pesticide-residue FV intake (Table 1 and Table S3). Intakes of low-pesticide-residue and high-pesticide-residue FVs were positively related to each other ($r_{Spearman}$ = 0.63 in NHS, 0.70 in NHSII, and 0.63 in HPFS).

In age-adjusted models, intakes of high- and low-pesticide-residue FVs were inversely associated with all-cause and cause-specific mortality (Table 2). In multivariable-adjusted analyses, however, intake of high-pesticide-residue FVs was unrelated to mortality whereas the inverse association for low-pesticide residue FV intake persisted (Table 2). Most of the change between the age-adjusted and the multivariate-adjusted models was a result of adjustment for physical activity. Relative to individuals consuming <1 serving of high-pesticide-residue FVs/day, the pooled multivariable-adjusted HRs (95% CI) for total mortality were 0.95 (0.92–0.99) for individuals consuming 1–1.9 servings/day, 0.97(0.92–1.02) for individuals consuming 2–3 servings/day, 1.01 (0.93–1.11) for individuals consuming 3–4 servings/day, and 0.93 (0.81–1.07) for individuals consuming $\geq$ 4 servings/day (P, trend = 0.84). The corresponding estimates for intake of low-pesticide-residue were: 1 (Reference), 0.81 (0.77–0.84), 0.72 (0.68–0.75), 0.65 (0.62–0.69), and 0.64 (0.59–0.68) (P for trend $\leq$ 0.001). This pattern was similar in analyses of cause-specific mortality (Table 2), when intake was modeled as quintiles (Table S4), in cohort-specific analyses (Table S5), when only deaths before age 70 years were considered (Table S6), and when only the most recent diet assessment was considered (Table S7). Interestingly, although intake of low-pesticide residue FV was inversely related to mortality from causes other than CVD, cancer and respiratory diseases, combined (Table 2), mortality from neurological diseases was unrealeated to intake of intake of either low- or high-pesticide residue FVs.

To gain further insights into the shape of the dose–response relation we then modeled intake of FVs as a continuous variable, allowing for non-linear relations (Fig. 1). In these models, the inverse relation of low-pesticide residue FV with all-cause (Fig. 1B), CVD (Fig. 1D), and respiratory mortality (Fig. 1H) plateaued at approximately a 50% reduction in mortality with an intake of 3.5 servings/day, whereas for cancer mortality the benefits were more modest but did not plateau within the observed range of intake (Fig. 1F). The picture was more complex for intake of high-pesticide-residue FV intake. For all-cause mortality, there was a statistically significant non-linear relation where intake of high-pesticide-residue FVs was related to lower mortality rates at modest intake levels, reaching a nadir at intakes of 1.5 servings/day, but without evidence of benefit at higher intake levels (Fig. 1A). This pattern was similar to that observed for cancer mortality (Fig. 1E), and respiratory mortality (Fig. 1G). On the other hand, intake of high-pesticide-residue FVs was completely unrelated to CVD mortality within the observed range of intake (Fig. 1C).

We then estimated the effect of substituting high-pesticide-residue FVs with low-pesticide-residue FVs (Figure S1). Consuming one daily serving of low-pesticide-residue FVs instead of a serving of high-pesticide residue FVs was associated with 11% lower risk of all-cause mortality (HR: 0.89; 95 %CI: 0.86–0.93). A similar pattern was observed in analyses for disease-specific mortality.

4. Discussion

We evaluated the association of high- and low-pesticide-residue FV intake with all-cause and cause-specific mortality in three large U.S. cohorts. We observed that intakes of FVs with low-pesticide-residue content were associated with lower risk of total mortality and cause-specific mortality. Specifically, consumptions of $\geq$ 4 servings/day of low-pesticide-residue FVs were linked to 36% lower risk of total mortality relative to consuming < 1 serving/day. Conversely, intake of high-

pesticide-residue FVs was unrelated to mortality, with some differences for cancer, CVD and respiratory disease mortality. On aggregate, these findings suggest that exposure to pesticide residues through diet may offset some of the well documented benefits of FV consumption on mortality, particularly for CVD mortality.

A recent *meta*-analysis found that intakes of FVs up to 800 g/day (10 servings/day) were associated with decreased risk of all-cause mortality. (Aune et al., 20172017) Another previous *meta*-analysis investigated the same relationship, reporting higher FV consumption reduced total mortality risk up to around 5 servings/day. (Wang et al., 2014) An inverse relationship was found for cardiovascular mortality whereas no association was reported for cancer mortality. Regarding respiratory disease, although we did not have a prior hypothesis regarding exposure to pesticides through diet in relation to this outcome, a *meta*-analysis showed FV intake protects against respiratory diseases, such as asthma. (Hosseini et al., 2017) An inverse relationship was also observed between dietary patterns with high plant-based foods and chronic respiratory mortality. (Neelakantan et al., 2018) Moreover, others have shown that diets favoring intake of fruits and vegetables are related to a lower risk of chronic obstructive pulmonary disease. (Varraso et al., 2015; Tabak et al., 2001; Varraso et al., 2010) The 2015 USDA Dietary Guidelines for Americans recommended intake of 4.5 servings/day from fruits and vegetables for adults consuming 2,000 calories/day. (U.s., December 2015) Our results for low-pesticide-residue FV intake suggest a benefit for total and disease specific mortality and are in line with these findings and recommendations.

Despite the consistency between our findings for low-pesticide-residue FVs with the existing literature, the divergent association of high-pesticide-residue FVs with mortality begs for an explanation. Confounding should be considered as a first potential explanation. However, not only were intakes of high- and low-pesticide residues positively related to each other in this study population but also each of these were associated with generally more healthy behaviors including healthier diets, greater engagement in physical activity and less smoking. Another potential explanation is that the nutritional profile of high- and low-pesticide-residue FVs is sufficiently different to result in different relations with mortality. This, however, proved not to be the case in this study population (Table S3). While we did not have direct biomarker measures of exposure to pesticides, we have previously shown that the classification method used in this study is related to biomarkers of exposure to pesticides in a clinical sample from Boston as well as in samples representative of the general population of the U.S. (Hu et al., 2016; Chiu et al., 2018) Based on these considerations, our interpretation of these findings is that the diverging relations of high- and low-pesticide-residue FV intake with mortality are attributable to pesticide contamination of these foods.

To our knowledge, no previous epidemiological study has directly examined the association between exposure to pesticide residues through diet and mortality. There are some studies; however, that have assessed associations with risk of major chronic diseases. Organic foods are less likely to have pesticide residues than conventionally grown foods due to the prohibition of synthetic pesticides by organic food standards. Moreover, interventions switching individuals from conventional to organic diets result in a dramatic decline in urinary pesticide metabolites. (Hyland et al., 2019; Baudry et al., 2019; Lu et al., 2006; Bradman et al., 2015; Oates et al., 2014) In the Nutri-Net Santé study, increasing consumption of organic foods was related to 25% lower cancer risk, driven by inverse relations with post-menopausal breast cancer and Non-Hodgkin lymphoma (NHL). (Baudry et al., 2018) However, in the Million Women Study, organic food intake was unrelated to cancer risk, although it was inversely related to NHL risk. (Bradbury et al., 2014) Using the same method for classifying FVs in the U.S. food supply according to their pesticide residues, we have previously reported no association between intake of low- or high-pesticide residue fruits and vegetables and cancer incidence, (Sandoval-Insausti et al., 2021) raising the question of whether exposure to pesticide
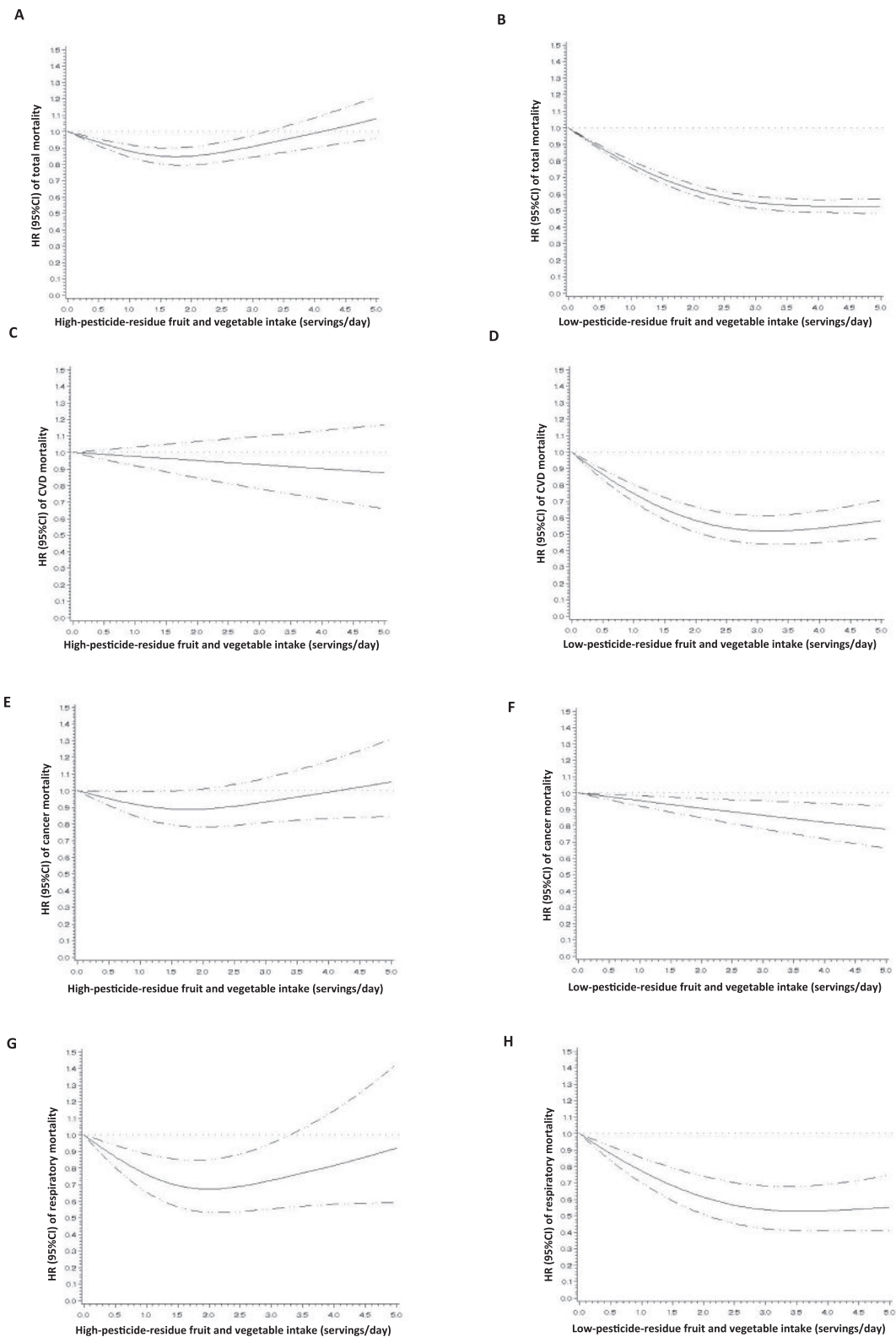
Fig. 1. Fruit and vegetable intake, considering pesticide residue status, and total mortality (panels A and B), CVD mortality (panels C and D), cancer mortality (panels E and F), and respiratory mortality (panels G and H). Adjusted for age, body mass index (quintiles), ethnicity (white/non-white), physical activity (quintiles), family history of cancer (yes/no), family history of cardiovascular disease (yes/no), smoking in package-years (never smoker, 1–4.9, 5–19.9, 20–39.9, or ≥ 40), postmenopausal hormone use (premenopausal/never/past/current, in NHS and NHSII), baseline hypertension (yes/no), baseline hypercholesterolemia (yes/no), total energy intake (quintiles), alcohol intake (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, or ≥ 30 g/day), and Alternate Healthy Eating Index score excluding criteria for intake of fruits and vegetables and alcohol (quintiles). Panels A,C,E,G are additionally adjusted for intakes of low-pesticide-residue fruits and vegetables (servings/day) and other fruits and vegetables with undetermined residues(servings/day). Panels B,D,F,H are additionally adjusted for intakes of high-pesticide-residue fruits and vegetables (servings/day) and other fruits and vegetables with undetermined residues(servings/day).

residues through diet may be related to disease progression, rather than incidence. This scenario would be consistent with our observations of no elevated risk of cancer but increased cancer mortality, is consistent with previous findings on the relation between diet and incidence of common malignancies, (Chavarro et al., 2008) and should be evaluated in future studies. Also of relevance to our finding of a divergent association pattern for low and high-pesticide residue intake with mortality, we previously reported an inverse association of low-pesticide-residue FV intake with coronary heart disease but no relation between high-pesticide-residue FV intake with this outcome, (Chiu et al., 2019) mirroring our findings for CVD mortality. We have also reported the same pattern of association for different reproductive outcomes, including successful infertility treatment and markers of spermatogenesis (Chiu et al., 2018; Chiu et al., 2015; Chiu et al., 2016).

The mechanisms underlying these findings have not been reported yet in humans. Concerning animal research, (Gibert and Sargis, 2020) long-term gestational and lactational exposure to six pesticides (Cyromazine, MCPB, Pirimicarb, Quinoclamine, Thiram, and Ziram) was related to metabolic disorders in rats. (Svingen et al., 2018) Likewise, chronic ingestion of six pesticides (boscalid, captan, chlorpyrifos, thiofenate, thiacloprid, and ziram) was associated with metabolic disruption in mice. (Lukowicz et al., 2018) Long-term exposure to eleven pesticides, including pesticides found on food samples, was linked to body weight gain and hepatotoxic parameters in rats. (Docea et al., 2018) In vitro, the incubation for 48 h of McA rat hepatoma cells with chlorpyrifos promoted hepatic steatosis, by increasing lipid accumulation and decreasing triglycerides secretion. (Howell et al., 2016) Nevertheless, no previous animal or in vitro study has tested the effects of dietary pesticide exposure on mortality.

Our study has notable strengths. This is the first epidemiological study that we know of to assess associations between dietary pesticide exposure and mortality. Diet was measured repeatedly with a validated tool during 20 years of follow-up, (Rimm et al., 1992; Yuan et al., 2018; Yuan et al., 2017) and cumulative average intakes were calculated to mitigate within-subject variation. Furthermore, we had a large sample size and number of deaths, providing enough statistical power and allowed to examine different causes of mortality. Some limitations should be noted. First, dietary pesticide exposure was not quantified directly in each participant but obtained by matching self-reported FV intake from FFQ with pesticide residue surveillance data. Second, we could not take into account whether FVs were conventionally grown or organic. Third, it was not possible to match some FVs in the FFQ with the corresponding item in the pesticide surveillance data, particularly in the early years of follow-up when the PDP had yet to collect information on most produce available in the U.S. This could lead to certain misclassification and lack of specificity of pesticide exposure. However, we created a category of undetermined-pesticide-residue FVs we adjusted for in multivariable analyses. Fourth, the PRBS prioritizes the assesment of overall food contamination with pesticides rather than contamination with specific compounds. This may result in observed associations that are weaker than true associations, especially if associations are driven by only one or a small number of specific pesticides and contamination with the causally-relevant pesticide is only weakly related to overall contamination. Although we cannot rule out this possibility, we do know that the overall contamination score correlates well with markers of exposure to organophosphates, organochlorides and 2,4-D. Additional limitations related to the PRBS include the fact that it does not take into consideration cooking methods, which could affect exposure to pesticide residues, and that if focuses exclusively on intake of fruits and vegetables, which are the most important –but not the only– source of pesticide residues in the diet. Fifth, as in most nutritional epidemiological studies, diet was self-reported and measurement error cannot be dismissed. Sixth, some residual confounding cannot be ruled out. However, results remained unchanged after several sensitivity analyses and after adjusting for a large number of potential confounders, including variables associated with the exposure or the outcome in the literature. (Ding et al., 2019)

In conclusion, low-pesticide-residue FV intake was inversely related to mortality whereas high-pesticide-residue FV intake was unrelated to mortality, suggesting pesticide residues may modify the beneficial effect of FV intake on mortality. Nevertheless, given the paucity of data on this topic, more studies should be performed in order to provide further evidence on the long-term health effects of pesticide exposure through diet. Additional evaluation in independent studies is particularly important for respiratory disease mortality and for mortality due to causes other than CVD, cancer or respiratory diseases, since the priors for these two broad disease categories were significantly weaker than the priors regarding CVD and cancer mortality.

CRediT authorship contribution statement

Helena Sandoval-Insausti: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Writing – original draft. **Yu-Han Chiu:** Methodology, Supervision, Validation, Visualization, Writing – review & editing. **Yi-Xin Wang:** Validation, Visualization, Writing – review & editing. **Jaime E. Hart:** Validation, Visualization, Writing – review & editing. **Shilpa N. Bhupathiraju:** Validation, Visualization, Writing – review & editing. **Lidia Mínguez-Alarcón:** Validation, Visualization, Writing – review & editing. **Ming Ding:** Validation, Visualization, Writing – review & editing. **Walter C. Willett:** Validation, Visualization, Writing – review & editing. **Francine Laden:** Validation, Visualization, Writing – review & editing. **Jorge E. Chavarro:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.107024.

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