Preventive Medicine Reports 42 (2024) 102742

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: www.elsevier.com/locate/pmedr

The clustering effects of current smoking status, overweight/obesity, and physical inactivity with all-cause and cause-specific mortality risks in U. S. adults

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ARTICLE INFO

Keywords:
Smoking status
Body mass index
Physical activity
Mortality risk
Rate advancement period
NHANES
Survey
USA

ABSTRACT

Objective: To estimate the associations of smoking, weight status and physical inactivity with all-cause and cause-specific deaths, and the advanced rate period (RAP) to determine how early death was advanced among United States (U.S.) adults aged 18 years or older.
Methods: We used data from the third National Health and Nutrition Examination Survey (NHANES III) and the 2019 Linked Mortality File (LMF) with a follow-up period of 21.6 years (n = 16,612, including 7,278 deaths). Smoking, weight status, and physical inactivity were obtained from NHANES III and mortality outcomes from the 2019 LMF. Cox regression was used to estimate hazard ratios, RAPs and their corresponding confidence intervals.
Results: For adults who currently smoke, were obese and physically inactive, the rate of dying from all-cause, CVD, and cancer was at least 231 % greater than for those who never smoked, were normal weight and physically active. The RAPs associated with the clustering of these risk factors for all cause, CVD- and cancer-specific cause of deaths were 13.0, 12.1 and 18.9 years older, respectively.
Conclusions: Our findings underscore the need to focus on modifiable risk factors for illness prevention and health promotion and call attention to the increasing clustering of unhealthy risk factors in the U.S. population.

1. Introduction

The significant decline in smoking prevalence among adults in the United States (U.S.) is a laudable achievement in public health. While there was a decline of more than 20 % in U.S. adults who smoked between 1964 and 2014 (National Center for Chronic Disease Prevention and Health Promotion, 2014), the prevalence of current smoking continued to decline from 20.9 % in 2005 to 11.5 % in 2021 (Cornelius et al., 2023). Nevertheless, despite this significant decline, more than 480,000 deaths per year are attributable to smoking alone, thereby posing an important public health threat (Lariscy et al., 2018). Life expectancy among adults who smoke is also at least 10 years shorter than among non-smoker adults (Jha et al., 2013) and is associated with heart disease, stroke, and some cancers (Smoking & Tobacco Use, 2023).

Similarly, other chronic health conditions and behaviors such as overweight, obesity, and physical inactivity are leading causes of death in the U.S. Currently, 30.7 % of U.S. adults are classified as overweight and 42.4 % as obese (Fryar et al., 2020), with the United States having the highest share of adults with obesity among developed nations (Obesity and the Economics of Prevention, 2023). A large body of evidence has shown that physical inactivity is associated with all-cause and cause-specific deaths, including cancer deaths (Katzmarzyk et al., 2022). Current guidelines recommend that adults engage in 150 minutes of moderate or vigorous physical activity, or a combination of the two, on a weekly basis (Physical Activity, 2023). However, less than 40 % of the U. S. population meets these recommendations (CDC, 2023; Physical Activity, 2023) and roughly 25 % of U.S. adults are not active at all.

While each of these health conditions and behaviors alone warrants continued public health prevention efforts, most research has only considered the occurrence of these health conditions separately, with few studies examining how clustering of risk factors influences morbidity and mortality outcomes (Islami et al., 2018; Liang et al., 2023; Rosella et al., 2019), and whether clustering of risk has a stronger effect on all-cause and/or cause-specific mortality risks than having none or

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https://doi.org/10.1016/j.pmedr.2024.102742
Received 5 February 2024; Received in revised form 20 April 2024; Accepted 22 April 2024
Available online 26 April 2024

only one chronic health condition (Loef and Walach, 2012; Choi et al., 2022; Borrell, 2014). For example, a meta-analysis of 15 studies examining the clustering effects of healthy lifestyle behaviors (never smoker, no alcohol consumption, physical activity, healthy diet, and normal weight) on all-cause mortality risk found that, for individuals with at least four healthy behaviors, the risk of dying was 66 % lower than that of their counterparts with at least one unhealthy behavior (Loef and Walach, 2012). Moreover, in a previous study, we found that the joint effect of smoking, physical inactivity, and obesity was associated with earlier all-cause and cardiovascular disease-specific mortality risks among U.S. adults who participated in the third National Health and Nutrition Examination Survey (NHANES) and were followed up until 2006 (Borrell, 2014). In the present study, we updated this analysis to include a longer follow-up period through 2019 and added cancer-specific mortality as an outcome, given increasing evidence on the association between physical inactivity and weight status across multiple types of cancers (Rock et al., 2020; McTiernan et al., 2019; Rezende et al., 2018). Thus, we examined the independent and combined associations of current smoking, weight status, and physical inactivity with all-cause, cardiovascular disease (CVD)-, and cancer-specific deaths, and the advanced rate period of dying associated with the clustering of these exposures in U.S. adults aged 18 years or older.

2. Methods

We used two publicly available datasets: the third National Health and Nutrition Examination Survey (NHANES III) and the 2019 National Death Index Linked Mortality File (LMF) (Public-Use Linked Mortality Files, 2019). NHANES III is a national survey using a multistage stratified probability sample conducted from 1988 to 1994 assessing the health status of a representative sample of the civilian non-institutionalized US population (Sample Design and Analysis Guidelines, 1994). Briefly, NHANES uses a stratified multistage probability design consisting of three stages: 1) primary sampling units, 2) segments composed of city or suburban blocks or combinations of blocks, and 3) households and certain types of group quarters, such as dormitories. We linked NHANES III data from the household adult examination and laboratory datasets with the 2019 LMF (n = 20,050) (Public-Use Linked Mortality Files, 2019). Matching of records was performed by the National Center for Health Statistics using a standard probabilistic algorithm via social security number, first name, middle initial, last name or surname, month, day, and year of birth, sex, father's surname, state of birth, race, state of residence, and marital status to link the records of the LMF to NHANES III participants (National Center for Health Statistics, 2006).

2.1. Outcome variable

We used the all-cause mortality status specified in the LMF dataset, where the underlying cause of death (UCOD) was determined using the International Classification of Diseases (ICD), Ninth and Tenth Revisions (Anderson et al., 2001) to classify CVD-specific mortality status. Specifically, CVD-specific deaths were determined using UCOD codes 001 and 005, and cancer-specific deaths were determined using UCOD code 002. Time at risk of death was calculated in person-years as follows: For participants who died, from the interview date to the date of death, whereas for those who were alive, from the interview date to December 31, 2019 (Data Linkage Team, 2010).

2.2. Exposures

Smoking status was defined in NHANES III using two self-reported questions: "Have you smoked 100 cigarettes in your lifetime?" and, "Do you smoke now?" with possible answers of yes/no. Categories were determined as follows: current smokers were defined as participants responding positively to both questions; former smokers were defined as respondents who said "Yes" to the first and "No" to the second question; and never smokers were participants who responded "No" to the first question. Body mass index (BMI), measured in NHANES III as the ratio of weight in kilograms and height in meters squared (kg/m^2), was categorized as follows: <25.0 kg/m^2 (normal weight), 25.0 kg/m^2 to < 30.0 kg/m^2 (overweight), and ≥ 30.0 kg/m^2 (obesity). Leisure-time physical activity (LTPA) in the past month was specified using the following questions: "In the past month, did you…: jog or run; ride bicycle/exercise bicycle; swim; do aerobics or aerobic dancing; do other dancing, do calisthenics or exercises; do garden/yard work; lift weights; or any other exercises or sports?" with participants responding "yes" to any of these activities considered physically active during their leisure time. Further, a three-category definition was created to capture the weekly frequency of reported physical activities by classifying participants as inactive (0–1 activity/week), infrequently active (1–5 activities/week), and active (5 + activities/week) (Borrell, 2014).

Consistent with a previous study, (Borrell, 2014) we examined the combined or clustering effects of current smoking status, overweight/obesity, and physical inactivity. We classified individuals across different combinations but focused on the following categories: 1) individuals with three unhealthy risk factors: a) current smoker, obese, and physically inactive; and b) current smoker, overweight, and physically inactive; 2) those with two risk factors, including current smoker; 3) those with two unhealthy risk factors and either never or former smokers; and 4) never smoker, normal weight, and physically active (reference category).

2.3. Covariates

Consistent with previous studies (Liang et al., 2023; Loef and Walach, 2012; Borrell, 2014), we adjusted for age, sex at birth, race/ethnicity, marital status, nativity status, and education. For analytical purposes, age was considered continuous and categorical (18–29, 30–44, 45–64, and > 65 years), whereas sex was considered as collected (male/female). Race/ethnicity was self-identified by NHANES participants as non-Hispanic white, non-Hispanic Black, and Mexican American. Marital status was classified as married, divorced, single, and widowed. Nativity status was specified as U.S.- and foreign-born. Education was specified as less than a high-school diploma or general equivalency diploma (GED), high-school diploma or GED, and more than high-school diploma or GED.

Out of the total sample (n = 20,050), we excluded records of individuals who were: <18 years of age at the time of the interview (n = 432); ineligible for follow-up (n = 19); women who reported being pregnant (n = 263); who reported a race/ethnicity as "other" (n = 698); and without information on BMI (n = 1,860), mortality status (n = 9), education (n = 113), smoking status (n = 1), nativity status (n = 29) and marital status (n = 14). These exclusions yielded a final sample of 16,612 including 7,278 deaths and approximately 359,235.17 person-years (median = 21.6, range: 0.1 to 26.2 years).

2.4. Statistical analysis

Descriptive statistics were calculated for the overall population and by mortality status. We calculated the prevalence of smoking, BMI categories, physical inactivity, and their combined or clustered effects as death rates for all-cause, CVD- and cancer-specific mortality in the total population. Cox proportional hazard regression was used to estimate hazard ratios (HR) and 95 % confidence intervals (CI) for all-cause, CVD- and cancer-specific mortality risks associated with each risk factor (smoking status, BMI categories, and physical inactivity) and their combined or clustered effects before and after controlling for age, sex, race/ethnicity, marital status, nativity status, and education. Models for BMI categories were adjusted for LTPA and smoking, models for smoking status were adjusted for BMI categories and LTPA, and models for LTPA were adjusted for BMI categories and smoking status. For CVD- or

Table 1
Distribution of selected characteristics [a] of US adults aged 18 years or older and by mortality status: Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994)-Linked Mortality Files 2019.

Characteristics		Alive	Dead	Total
	N = 16,612	% (SE)[a]	% (SE)	% (SE)
Age, mean years (SE)		35.8 (0.29)	60.9 (0.55)	44.4 (0.50)
18–29	3,834	34.2 (1.17)	4.4 (0.47)	23.8 (0.89)
30–44	4,547	44.5 (1.17)	12.4 (0.76)	33.4 (1.00)
45–64	3,904	20.1 (0.81)	35.8 (1.12)	25.5 (0.64)
≥65	4,327	1.2 (0.16)	47.3 (1.72)	17.2 (0.93)
Sex[b]				
Male	7,893	48.2 (0.53)	48.8 (0.74)	48.4 (0.38)
Female	8,719	52.8 (0.53)	51.2 (0.74)	51.6 (0.38)
Race/ethnicity				
Non-Hispanic white	7,193	81.1 (1.04)	85.2 (0.84)	82.5 (0.85)
Non-Hispanic Black	4,813	12.2 (0.81)	11.4 (0.76)	11.9 (0.72)
Mexican American	4,606	6.7 (0.58)	3.4 (0.20)	5.5 (0.44)
Marital Status				
Married	9,483	63.9 (1.11)	61.1 (0.97)	62.9 (0.86)
Divorced	2,078	11.4 (0.64)	12.0 (0.69)	11.6 (0.49)
Single	3,139	23.5 (1.05)	7.9 (0.61)	18.1 (0.86)
Widow	1,912	1.2 (0.13)	19.0 (0.71)	7.4 (0.38)
Nativity Status				
U.S.-born	13,604	90.8 (0.78)	94.2 (0.48)	92.0 (0.61)
Foreign-born	3,008	9.2 (0.78)	5.8 (0.48)	8.0 (0.61)
Education				
Less than high school	6,927	17.4 (0.90)	38.0 (1.37)	24.5 (1.04)
High school/GED	5,128	35.7 (0.90)	33.0 (0.73)	34.7 (0.69)
More than high school	4,557	46.9 (1.37)	29.9 (1.13)	40.7 (1.27)

[a] Proportions (standard errors);
[b] Pregnant women were excluded.

cancer-specific mortality analysis, deaths due to other causes were treated as censored. To determine how much time the rate of death was advanced among exposed compared with their non-exposed counterparts (Brenner et al., 1993; Discacciati et al., 2016), we calculated the rate advancement period (RAP) and its 95 % CIs for each outcome using the coefficients for age and each exposure in the adjusted models. RAP represents the age difference to reach the same rate of dying between adults who are exposed and unexposed, assuming an increased death rate with age (Brenner et al., 1993; Discacciati et al., 2016). No violation of Cox proportional assumptions via Schoenfeld residuals was observed (Grambasch and Therneau, 1994).

All data management and analyses were conducted with SAS 9.4 for Windows (SAS Institute Inc. Cary, NC). Sample sizes presented in Table 1 were unweighted, the rest of the estimates were weighted.

3. Results

Overall, the mean age of the study population was 44.4 years with one-third of adults being 30 to 44 years old, mostly non-Hispanic white (82.5 %) and U.S.-born (92 %); more than half were female (51.6 %), married (63 %), and most had at least a high school education (75.4 %; Table 1). Similar patterns were observed when compared adults who died and those who did not die at the end of the follow period with the exception of age with those who died being older (60.9 years versus 35.8 years) and widows (19 % versus 23.5 % single), and having less than a high school diploma (38 % versus 46.9 % more than a high school diploma).

Almost one-third of the population reported being current smokers (29.2 %) and being active (31.2 %), and more than half of the population were classified as overweight or obese (54.3 %; Table 2). In addition, 5.5 % of adults engaged in a combination of all three unhealthy risk factors, and 22.8 % in two. The rates of death from all-cause, CVD- and cancer-specific causes were the highest for adults reporting being former smokers, classified as obese, and reporting being physically inactive. When considering the clustered effects of these factors, adults who were current smokers, obese, and physically inactive had the highest mortality rates for all-causes (2564.4 per 100,000), CVD-specific (804.2 per 100,000), and cancer-specific causes of death (644.0 per 100,000).

Being a current or former smoker, overweight or obese, and physically inactive was associated with an all-cause mortality rate of at least 22 % (Table 3). After adjusting for age, sex, race/ethnicity, marital status, nativity status, educational attainment, BMI categories, and physical activity (BMI categories and smoking status models only), adults who reported being current or former smokers had a 2.16 (95 % CI: 1.98, 2.35) and 1.30 (95 % CI: 1.20, 1.40) greater rate of dying than those who never smoked. When compared with adults of normal weight, those who were obese had a 25 % greater rate of dying after full adjustment. Adults reporting being physically inactive had a 1.34 (95 % CI: 1.23, 1.46) greater rate of dying than their counterparts who were active after adjustment. When compared with adults who reported never smoking, being of normal weight, and physically active, those who currently smoked were obese and inactive had a 3.60 (95 % CI; 2.86, 4.53) higher rate of dying of any cause. This rate remained significant although attenuated after full adjustment: 3.31 (95 %CI: 2.56, 4.28).

Table 3 also shows the rates for the independent and combined associations of the exposures with CVD- and cancer-specific mortality risks. Former smoking status, being at least overweight and physically inactive was associated with at least 55 % greater rate of dying of a CVD-specific cause. After controlling for selected characteristics, these associations were significant for current (HR:1.87, 95 %CI: 1.60, 2.19) and former (HR:1.21, 95 %CI: 1.07, 1.37) smoking status, obesity (HR:1.51, 95 %CI: 1.26, 1.80), and physical inactivity (HR:1.38, 95 %CI: 1.19, 1.61). When the combined or clustered effect of these risk factors was considered, adults who currently smoked were obese and physically inactive had a 3.37 (95 %CI: 2.19, 5.18) higher rate of dying of any CVD condition when compared with their counterparts who never smoked, were normal weight, and physically active. This association remained significant and slightly increased when controlling for age, sex, race/ethnicity, marital status, nativity status, and education: HR: 3.79 (95 % CI: 2.45, 5.88). As for cancer-specific mortality, adjusted associations were significant and stronger for current (HR:3.24, 95 %CI: 2.66, 3.94) and former (HR:1.54, 95 %CI: 1.27, 1.86) smoking status, but weaker for obesity (HR:1.22, 95 %CI: 1.01, 1.48) than the ones observed for CVD-specific mortality. Adults who currently smoked, were obese and

Table 2
Prevalence (weighted) of smoking, BMI categories, and physical activity, their combined effects and death rates for all-cause, cardiovascular disease (CVD) and cancer-specific mortality for US adults aged 18 years or older: NHANES III (1988–1994)-Linked Mortality Files 2019.

Characteristics			All Cause	CVD-Specific	Cancer-Specific
	N = 16,612	Prevalence % (SE)[a]	Number of deaths (Rates/ 100,000 persons-years)	Number of deaths (Rates/ 100,000 persons-years)	Number of deaths (Rates/ 100,000 persons-years)
Total			7,278 (1476.3)	2,756 (506.9)	1,558 (351.0)
Smoking status					
Current	4,274	29.2 (0.83)	1,791 (1409.6)	540 (384.6)	517 (450.6)
Former	4,097	25.8 (0.56)	2,449 (2185.0)	969 (781.3)	525 (495.3)
Never	8,241	45.0 (0.76)	3,038 (1159.6)	1,247 (445.9)	516 (214.9)
Body mass index categories					
Normal	6,729	45.7 (0.85)	2,643 (1157.6)	949 (362.9)	574 (281.4)
Overweight	5,682	32.1 (0.57)	2,657 (1629.3)	1,019 (561.6)	590 (398.5)
Obese	4,201	22.2 (0.66)	1,978 (1961.5)	788 (747.7)	394 (436.0)
Any leisure-time physical activity					
Yes	11,495	79.2 (0.88)	4,511 (1270.1)	1,630 (418.7)	1042 (317.5)
No	5,117	20.8 (0.88)	2,767 (2399.3)	1,126 (904.2)	516 (502.0)
Weekly number of activities					
Inactive (1–0)	8,237	38.8 (1.28)	4,070 (1913.9)	1,608 (700.6)	813 (427.1)
Infrequently active (1−<5)	3,945	30.2 (0.54)	1,417 (1136.7)	492 (349.1)	344 (291.9)
Active (≥5)	4,430	31.2 (1.09)	1,791 (13154)	656 (442.4)	401 (323.1)
Combined Effect[b]					
Current smoker, obesity, and physically inactive	507	2.4 (0.21)	260 (2564.4)	87 (804.2)	65 (644.0)
Current smoker, overweight, and physically inactive	685	3.1 (0.21)	325 (1702.8)	119 (541.5)	78 (478.7)
Current smoker with either physical inactive or overweight/obesity	1495	8.7 (0.41)	667 (1470.6)	184 (378.2)	201 (519.2)
Physical inactive and overweight/ obesity and never smoker	2644	9.2 (0.37)	1173 (1751.1)	503 (733.5)	197 (304.9)
Physical inactive and overweight/ obesity and former smoker	1328	5.4 (0.30)	865 (3002.1)	361 (1156.5)	168 (635.4)
All others	8884	52.3 (0.94)	3700 (1351.9)	1389 (460.0)	805 (318.8)
Never smoker, normal weight, and physically active	1069	7.1 (0.39)	288 (739.9)	113 (240.4)	44 (136.2)

[a] Prevalence (standard error);
[b] For the joint effect, physical inactivity was specified using the three-category definition (inactive [0–1 activity/week], infrequently active [1–5 activities/week] and active [5+ activities/week]). The "all others' category includes any combination other than the ones presented here.

physically inactive had a 4.92 (95 % CI: 3.26, 7.43) greater rate of dying from cancer relative to adults who never smoked, were normal weight, and physically active. This estimate was 4.26 (95 % CI: 2.63, 6.88) after full adjustment.

The advancement rate period associated with the combined effects of current smoking, obesity and physical inactivity on all-cause death was 13.0 (95 % CI: 10.4, 15.6) years. This means that, on average, adults with this cluster of conditions are expected to advance their death by 13.0 years compared with those who never smoked, had normal weight, and were physically active (Fig. 1). For example, a 45 year-old adult who smoked, was obese and physically inactive is expected to experience the same rate of dying of any cause as a 58 year old adult who never smoked, had a normal weight, and was physically active. A similar pattern was observed for CVD-specific mortality. The RAP associated with these health conditions is expected to advance CVD- and cancer-specific deaths by 12.1 (95 % CI: 8.3, 15.9) and 18.9 (95 % CI: 12.9, 24.9) years, respectively, among adults who currently smoked, were obese and physically inactive compared with those who did not smoke, were normal weight and were physically active.

4. Discussion

Consistent with our previous work (Borrell, 2014), our study showed that smoking, obesity, and physical inactivity were associated with an increased rate of death from all-cause and CVD- or cancer-specific causes of death, after controlling for selected characteristics. Specifically, the clustering of these risk factors showed that among adults who reported being current smokers, were obese, and physically inactive, the rate of dying from all-causes was 3.31 greater than for those who reported never smoking, were of normal weight, and physically active. The rate of death due to CVD- and cancer-specific causes was at least 3.79. Finally, adults who reported being current smokers, physically inactive, and obese experienced deaths of any cause, CVD- and cancer-specific cause of death comparable to their counterparts who were 13.0, 12.1 and 18.9 years older, respectively.

Like a previous study (Cook et al., 2022), we found that anywhere from 20-40 % of the U.S. adult population was currently smoking, obese, or physically inactive, but less than 7 % of the U.S. adult population were non-smokers, normal weight, and physically active. A common analytic approach in the literature is to examine the co-occurrence of risk factors (also known as 'multimorbidity') by creating a total sum score of disease status, or classifying this score into categories of risk (e.g., 'high', 'medium', 'low') (Mossadeghi et al., 2023). As noted by Tsai and Venkataramani, modeling of disease in this way is valuable for identifying the additive effect of risk factors on disease (Tsai and Venkataramani, 2016). However, this analytic approach fails to capture the potential effect of how these risk factors interact to shape disease beyond their individual effects on health. In our study, we used a "combined or clustered effects" approach to determine how smoking, obesity, and physical inactivity jointly exacerbated the risk of death. For example, we found that the adjusted mortality risk associated with each risk factor independently ranged from 1.2 to 3.24. In contrast, when examining smoking, obesity, and physical inactivity jointly, we observed a 4-fold increased risk of death compared with individuals who were non-smokers, normal weight, and physically active. Our findings are consistent with those of a previous systematic review (Loef and Walach, 2012) including U.S. studies (van Dam et al., 2008; Byun et al., 2010; Ford et al., 2011). For instance, van Dam et al. found that the risk

Table 3
Unadjusted and adjusted hazard ratios (95 % confidence intervals) for smoking status, BMI categories, and physical activity, and their combined effects on all-cause, cardiovascular disease (CVD)- and cancer-specific mortality rates for US adults aged 18 years or older: NHANES III (1988–1994)-Linked Mortality Files 2019.

	All Cause		CVD-Specific		Cancer-Specific	
Characteristics	Unadjusted[a]	Adjusted[b]	Unadjusted	Adjusted	Unadjusted	Adjusted
Smoking status						
Current	1.22 (1.12, 1.33)	2.16 (1.98, 2.35)	0.86 (0.75, 0.99)	1.87 (1.60, 2.19)	2.10 (1.77, 2.50)	3.24 (2.66, 3.94)
Former	1.92 (1.75, 2.10)	1.30 (1.20, 1.40)	1.76 (1.54, 2.00)	1.21 (1.07, 1.37)	2.34 (1.95, 2.82)	1.54 (1.27, 1.86)
Never	1	1	1	1	1	1
Body mass index categories						
Normal	1	1	1	1	1	1
Overweight	1.42 (1.30, 1.55)	0.94 (0.86, 1.03)	1.55 (1.33, 1.80)	1.00 (0.86, 1.17)	1.43 (1.21, 1.70)	1.01 (0.84, 1.21)
Obese	1.72 (1.56, 1.91)	1.25 (1.11, 1.40)	2.07 (1.73, 2.47)	1.51 (1.26, 1.80)	1.58 (1.30, 1.93)	1.22 (1.01, 1.48)
Any leisure-time physical activity						
Yes	1	1	1	1	1	1
No	1.93 (1.79, 2.09)	1.34 (1.23, 1.46)	2.17 (1.93, 2.44)	1.38 (1.19, 1.61)	1.62 (1.38, 1.90)	1.22 (0.99, 1.50)
Weekly number of activities						
Inactive (1–0)	1.47 (1.32, 1.64)	1.18 (1.08, 1.29)	1.49 (1.31, 1.70)	1.26 (1.08, 1.46)	1.34 (1.11, 1.61)	1.08 (0.88, 1.33)
Infrequently active (1-<5)	0.86 (0.78, 0.95)	0.96 (0.86, 1.07)	0.81 (0.68, 0.95)	0.93 (0.79, 1.11)	0.90 (0.72, 1.13)	0.94 (0.74, 1.20)
Active (≥5)	1	1	1	1	1	1
Combined Effect[b]						
Current smoker, obesity, and physically inactive	3.60 (2.86, 4.53)	3.31 (2.56, 4.28)	3.37 (2.19, 5.18)	3.79 (2.45, 5.88)	4.92 (3.26, 7.43)	4.26 (2.63, 6.88)
Current smoker, overweight, and physically inactive	2.35 (1.82, 3.04)	2.05 (1.68, 2.50)	2.26 (1.38, 3.72)	2.29 (1.34, 3.93)	3.60 (2.28, 5.67)	2.91 (1.81, 4.67)
Current smoker with either physical inactive or overweight/obesity	2.01 (1.64, 2.48)	2.27 (1.85, 2.80)	1.58 (1.13, 2.21)	2.10 (1.42, 3.10)	3.87 (2.44, 6.13)	3.97 (2.44, 6.47)
Physical inactive and overweight/ obesity and never smoker	2.42 (1.99, 2.95)	1.21 (1.10, 1.50)	3.07 (2.20, 4.27)	1.49 (1.05, 2.13)	2.30 (1.44, 3.67)	1.26 (0.78, 2.04)
Physical inactive and overweight/ obesity and former smoker	4.24 (3.34, 5.38)	1.66 (1.39, 2.00)	4.85 (3.51, 6.71)	1.92 (1.40, 2.62)	4.89 (3.02, 7.93)	2.00 (1.22, 3.26)
All others	1.85 (1.56, 2.20)	1.20 (1.10, 1.50)	1.92 (1.42, 2.60)	1.37 (0.99, 1.89)	2.37 (1.50, 3.76)	1.65 (1.07, 2.61)
Never smoker, normal weight, and physically active	1	1	1	1	1	1

[a] Association of smoking status and physical activity with all-cause and CVD (Unadjusted).
[b] Hazard rates (HRs) adjusted for age, sex, race/ethnicity, marital status, nativity status, and education. Models for smoking status were additionally adjusted for BMI and physical activity; for BMI categories, adjusted for smoking status and physical activity; and for physical activity, adjusted for smoking status and BMI categories.

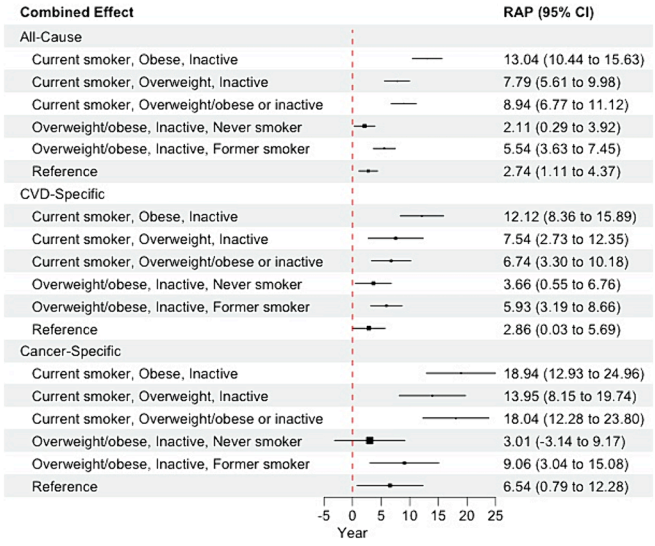

Fig. 1. Rate advancement periods (RAP) and 95% confidence intervals (CI) for all-cause, cardiovascular disease (CVD)- and cancer-specific mortality associated with the combined effects of smoking status, physical activity, and BMI categories for US adults aged 18 years or older: NHANES III (1988–1994)-Linked Mortality Files 2019. Reference: Never smoker, normal weight and physically active.

associated with all-cause, CVD- and cancer-specific mortality was at least 226 % greater among adults who reported cigarette smoking, being overweight, being physically inactive, drinking alcohol, and having a poor diet than among those without these conditions (van Dam et al., 2008). A similar finding was reported by McCullough et al., independent of sex (McCullough et al., 2011). These findings suggest the continued importance of recognizing the burden of multiple risk factors on health and, from a causal perspective, raise important avenues for future research to test the effectiveness of interventions that simultaneously address the additive or multiplicative effects of two or more risk factors to improve survival (VanderWeele and Knol, 2014). Thus, our findings call attention to programs and interventions focusing on modifiable risk factors and health conditions early in life. The latter is even more important given the changes observed in these factors and conditions during and post-COVID-19 (Ramalho et al., 2021; Martinez-Cao et al., 2021; Koopmann et al., 2021; Brener et al., 2022; Restrepo, 2022; Amini et al., 2021).

Our findings are generally consistent with those of our previous work examining the combined effect of current smoking, obesity, and physical inactivity on all-cause and CVD-specific mortality risk in advancing death using only 12 years of follow up (Borrell, 2014). Specifically, in the current study, after 22.5 years of follow-up, we found that individuals who currently smoked, were obese, and were physically inactive advanced their death associated with all- and CVD-specific causes by 13.0 and 12.1 years, respectively, compared with those who never smoked, had normal weightnon-obese, and were physically active.

These results were comparable to those observed in the earlier study showing 14.2 and 12.2 years of advanced rate periods associated with all- and CVD-specific causes, respectively. However, in the present study, we additionally examined cancer-specific deaths and found that these risk factors advanced cancer-specific deaths by 19.3 years, suggesting a pronounced effect of these exposures on cancer mortality. This large increase in advancing cancer-specific deaths merits immediate attention in developing targeted prevention interventions to curb the development of obesity and the adoption of smoking and sedentary lifestyle. Critically, the reduction in these chronic health conditions will require investment in initiatives that can create healthy environments to support more active living and reduce obesity and smoking (Dankwa-Mullan et al., 2010; Solar and Irwin, 2023).

Our study is not without limitations. First, we included all deaths, regardless of timing. The proportion of deaths occurring before three years was approximately 10 % for all-cause, CVD- and cancer-specific causes. We repeated the analyses excluding deaths occurring before 3 years, and the results remained significant but were stronger for all-cause mortality and slightly weaker for CVD- and cancer-specific mortality than those in Table 3. Second, our findings may be affected by competing risks for cause-specific findings and may bias our results. Third, given the self-reported nature of smoking status and physical activity, our results may be biased. However, self-reported smoking status in NHANES has been highly correlated with serum cotinine levels in smokers (92.5 %) and non-smokers (98.6 %). (Caraballo et al., 2001) Fourth, our exposures were measured at baseline 20 years ago. We may have missed changes in exposure status, which may have under- or overestimated our results. Fifth, we did not control for other variables that may have influenced the observed associations, such as alcohol consumption. However, we repeated the analyses adding alcohol consumption among the control variables, and the estimates did not change much relative to those presented in Table 3 (see Supplemental Table). Sixth, we used the publicly available NHANES-LMF dataset which contained limited information and perturbations for a small, selected number of records relative to the restricted version of the dataset. However, a comparative study of both datasets found similar results for all-cause mortality and selected cause-specific mortality risks, including CVD and cancer (Data Linkage Team, 2010). Therefore, it is unlikely that the use of the public dataset affected our results. Seventh, we may have missed NHANES participants who did not agree to participate. These individuals may have differed from those who participated in the study. However, this refusal may have been non-differential, leading our estimates towards the null. Lastly, we did not examine interaction among the exposures or with race/ethnicity. However, clustering the effects of smoking status, overweight/obesity, and physical activity provides a single estimate, and avoids issues related to underpowered analyses and interpretations when dealing with interactions. Moreover, given the additional social stressors racialized minoritized groups face in the U.S., we may have masked the deleterious coping effects of psychosocial stress associated with racial discrimination on health behaviors across the racial/ethnic groups included in the analyses (Borrell et al., 2010; Borrell et al., 2007; Borrell et al., 2013). Consistent with novel methods (Nieves et al., 2023; Evans et al., 2023), future research should examine the effects of the intersection of multiple exposures together with race/ethnicity and other social identities (i.e., age, education, sex/gender, and nativity status) on health outcomes.

Despite these limitations, our study included a large nationally representative sample of the two major racial/ethnic groups, non-Hispanic Black and white adults, as well as the largest Hispanic/Latino subgroup, Mexican Americans. In addition, we used a long follow-up period of approximately 22 years. Moreover, to the best of our knowledge, this is the first study to examine the combined effects of smoking, BMI categories, and physical inactivity on cancer-specific mortality risk. Finally, the calculation of the rate advancement period provides clues regarding the clustering effects of unhealthy and modifiable risk factors on an individual's death and survival prospects.

Our findings underscore the need to focus on well-known modifiable risk factors for health prevention and promotion and call attention to the increasing clustering of unhealthy risk factors in the U.S. population. These are preventable behaviors and conditions that begin to unfold early in life with high healthcare costs for population health. Thus, we must start promoting and addressing the contextual conditions leading to these behaviors early in life if we want to prevent their long-lasting effects on the health status of the population.

CRediT authorship contribution statement

Luisa N. Borrell: Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Sandra E. Echeverria:** Writing – review & editing, Writing – original draft, Investigation.

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.

Data availability

The data are publicly available at www.cdc.gov

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2024.102742.

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