A Large Cohort Study of Body Mass Index and Pancreatic Cancer by Smoking Status

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ABSTRACT

Background: Some evidence suggests the association between body mass index (BMI) and pancreatic cancer risk is weaker among current smokers than among never smokers.

Methods: We examined the association between BMI and pancreatic cancer mortality among adults who reported smoking status at enrollment into Cancer Prevention Study-II in 1982, including 420,543 never smokers, 282,244 former cigarette smokers, and 219,885 current cigarette smokers. After excluding the first 3 years of follow-up to reduce reverse causation, we calculated multivariable-adjusted hazard ratios (HR).

Results: During the full follow-up period from 1985 to 2014, 7,904 participants died of pancreatic cancer. The HR per 5 BMI units was lower among current smokers [HR = 1.14; 95% confidence interval (CI), 1.07–1.20] than never smokers (HR = 1.22; 95% CI, 1.17–1.27), although this difference was not statistically significant ($P = 0.06$). BMI was significantly less strongly associated with pancreatic cancer mortality among current smokers reporting ≥20 cigarettes/day (HR = 1.10; 95% CI, 1.03–1.18) than among never smokers. During follow-up within 10 years of enrollment, when current smokers at enrollment were the most likely to have still been smoking, BMI was not associated with pancreatic cancer mortality among current smokers (HR = 1.02; 95% CI, 0.90–1.16, $P = 0.03$ for difference between current and never smokers). BMI HRs were similar among former and never smokers.

Conclusions: These results support a weaker association between BMI and pancreatic cancer among current smokers than among never smokers.

Impact: In populations with low smoking prevalence, the pancreatic cancer burden due to BMI is likely to be higher than that predicted by risk estimates from studies including substantial numbers of smokers.

Introduction

The incidence of pancreatic cancer in the United States has been steadily increasing in recent years (1). The 5-year survival rate for pancreatic cancer remains low, approximately 9%, up from about 3% in the 1980s (2). Pancreatic cancer is now the third most common cause of cancer mortality in the United States and has been projected to become the second most common cause of cancer mortality by 2030 (3), highlighting the need to fully understand the impact of important risk factors for this disease.

Smoking and excess body weight are the two leading preventable causes of pancreatic cancer (4). Current cigarette smokers are at about 70% higher risk of pancreatic cancer than never smokers (5). Excess risk among former smokers declines with time since quitting, with little or no increase in risk compared with never smokers observable 20 or more years after quitting (5–7). Excess body weight is less strongly associated with pancreatic cancer than smoking is. In a large meta-analysis of prospective studies (8), each 5 kg/m^2 unit increase in body mass index (BMI) was associated with a 10% increase in risk of pancreatic cancer. However, excess body weight still contributes substantially to the burden of pancreatic cancer because of the very high prevalence of overweight and obesity in the United States and many other countries (9). A recent analysis estimated that about 17% of pancreatic cancer cases in the United States are due to excess body weight (4).

Some epidemiologic evidence suggests that excess body weight is associated with increased risk of pancreatic cancer among never and former smokers but not among current smokers. To our knowledge, three cohort analyses including 500 or more cases of pancreatic cancer have presented risk estimates for BMI stratified by never/former/current cigarette smoking status (10–12). In these analyses, BMI was generally associated with higher risk of pancreatic cancer among never and former smokers. In contrast, none of these studies observed an association with BMI among current smokers. Although this evidence is relatively consistent, it is based on a relatively limited number of cases. It therefore remains uncertain whether the association between BMI and risk of pancreatic cancer differs by smoking status, and if so, by how much. If the association between BMI and pancreatic cancer risk does differ by smoking status, there are potentially important implications both for individual risk prediction and for estimating the impact of excess body weight on population burden.

We examined whether the association between BMI and pancreatic cancer mortality differed by smoking status in CPS-II, a cohort with large numbers of never, former, and current smokers. The association between BMI and pancreatic cancer mortality in this cohort has been previously reported (13–15), but these reports did not focus on differences by smoking status.

Materials and Methods

Study population and follow-up

Subjects in this analysis were drawn from the 1,184,328 men and women in Cancer Prevention Study II (CPS-II). Participants were

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enrolled in 1982 by American Cancer Society (ACS) volunteers in all 50 U.S. states, the District of Columbia, and Puerto Rico as previously described (16). At enrollment in 1982, participants completed a four-page baseline self-administered questionnaire that asked about their current weight with indoor clothing and height without shoes, as well as about demographic characteristics and various behavioral, environmental, occupational, and medical factors, including detailed information on their smoking history. No updated information on weight, smoking, or other factors was collected after enrollment in 1982. CPS-II is approved by the Institutional Review Board of Emory University.

All analyses excluded participants who at enrollment reported a history of cancer other than nonmelanoma skin cancer ($N = 82{,}322$), were younger than age 30 or older than age 90 years ($N = 2{,}117$), had missing or relatively extreme BMI (<18.5 or >60 kg/m^2; $N = 45{,}691$), or had missing or uninterpretable smoking information ($N = 67{,}924$). In addition, participants whose smoking exposure could not be meaningfully classified based solely on their cigarette smoking status were excluded, which included participants who were never cigarette smokers but were current or former cigar or pipe smokers, and former cigarette smokers who were current cigar or pipe smokers ($N = 41{,}894$). Because our analysis excluded the first 3 years of follow-up (as described below), participants who died or were censored in the first 3 years of follow-up ($N = 21{,}708$) were also excluded, leaving 922,672 participants (383,746 men and 538,926 women) for analysis.

The vital status of study participants was determined through December 31, 2014, as previously described (17). Death certificates or codes for cause of death have been obtained for over 99% of all known deaths. Mortality follow-up was truncated at age 90 years because small percentages of deaths are missed by National Death Index linkage, which could result in significant misclassification of vital status at advanced ages that most participants do not survive to (18). The underlying cause of death was coded according to the 9th and 10th revisions of the International Classification of Disease (ICD-9 and ICD-10; ref. 19). Pancreatic cancer deaths were defined as ICD-9 codes 157.0–157.9 and ICD-10 codes C25.0–C25.9. This analysis could not be limited to exocrine pancreatic cancers, which account for approximately 97% of pancreatic cancers in the United States (20), because our mortality outcome data, derived from death certificates, do not routinely specify endocrine pancreatic cancer deaths as such.

Statistical analyses

We *a priori* excluded the first 3 years of follow-up to reduce bias from weight loss due to undiagnosed cancer, consistent with our previous analysis of BMI and pancreatic cancer mortality in CPS-II (15). We then used Cox proportional hazards regression modeling (21) to estimate HRs for pancreatic cancer mortality associated with a continuous measure of BMI. HRs for pancreatic cancer mortality from continuous models of BMI are consistent with HRs from categorical models in this study population (15). We ran separate models among never smokers, former smokers, and current smokers. All models were adjusted for age, sex, race, and education. Analyses among former or current cigarette smokers were additionally adjusted for reported cigarettes per day (<10, 10–<20, 20–<30, 30–<40, ≥40, and unknown). Among former smokers, further adjustment for years since quit, modeled as a time-dependent variable, had negligible influence on results. We adjusted for age by stratifying on single year of age at enrollment within each Cox model (22). All other covariates were modeled using the categories shown in **Table 1**. We did not adjust for diabetes in primary analyses because diabetes may often be on causal pathways between obesity and pancreatic cancer. We also conducted sensitivity analyses further adjusting for diabetes.

P values for differences between the BMI HR among former smokers or among current smokers compared with that among never smokers were calculated using the Wald-statistic for testing homogeneity (23). *P* values for trends in BMI HRs by years since baseline were calculated by modeling a multiplicative interaction term between a continuous variable for BMI and a continuous time-dependent variable for years.

To determine if the association between BMI and pancreatic cancer mortality among former or current smokers differed by cigarette dose, we stratified analyses by cigarettes per day (<20, ≥20). *P* values for trends in BMI HRs by cigarettes per day were calculated by modeling a multiplicative interaction term between a continuous variable for BMI and a continuous variable for cigarettes per day.

To determine if the association between BMI and pancreatic cancer mortality among former smokers differed by years since quit, we stratified analyses by years since quit (<10, 10–<20, 20–<30, and ≥30), modeled as a time-dependent variable initially defined by years since quit at enrollment, and extended until the participant died or was censored. The *P* value for a trend in the BMI HR by years since quit was calculated by modeling a multiplicative interaction term between a continuous variable for BMI and a continuous time-dependent variable for years since quit.

Results

Most participants in CPS-II were white and between the ages of 40 and 79 years at enrollment (**Table 1**). Compared with participants with a BMI of <25, those who were obese (BMI ≥ 30) were more likely to be black and less likely to be highly educated or a current smoker.

Table 2 shows associations between BMI and pancreatic cancer mortality among never, former, and current smokers, both during the full follow-up period from 1985 to 2014 and stratified by follow-up time. During the full follow-up period, BMI was associated with pancreatic cancer mortality among never smokers [HR = 1.22 per 5 BMI units; 95% confidence interval (CI), 1.17–1.27], former smokers (HR = 1.18; 95% CI, 1.12–1.25), and current smokers (HR = 1.14; 95% CI, 1.07–1.20, $P = 0.06$ for difference in BMI HR between current and never smokers). Results were similar in sensitivity analyses further adjusting for diabetes. During follow-up within 3 to 10 years of enrollment, BMI was associated with higher pancreatic cancer mortality in never smokers, whereas no association with BMI was observed among current or among former smokers [HR among current smokers: 1.02 (95% CI, 0.90–1.16), HR among former smokers: 1.03 (95% CI, 0.90–1.18)]. BMI HRs among both current and former smokers were statistically significantly different than that in never smokers during this early follow-up interval (*P* values of 0.03 and 0.04, respectively). However, a formal test of interaction using continuous variables for BMI and follow-up time (i.e., a test of proportional hazards) did not find differences in the BMI HR by follow-up time among never smokers ($P = 0.80$), former smokers ($P = 0.63$), or current smokers ($P = 0.34$).

Table 3 shows the association of BMI with pancreatic cancer mortality by number of cigarettes smoked per day among current smokers and former smokers, and by years since quit among former smokers. Among current smokers, there was some evidence for a weaker association between BMI and pancreatic cancer mortality among those reporting more cigarettes per day ($P = 0.06$ for trend). The HR for BMI among those reporting smoking ≥ 20 cigarettes per day (HR = 1.10; 95% CI, 1.03–1.18) was statistically significantly lower

Table 1. Pancreatic cancer risk factors by BMI at CPS-II enrollment in 1982.[a]

	BMI at enrollment		
	<25 kg/m^2 (n = 479,794) (%)	25–<30 kg/m^2 (n = 340,235) (%)	≥30 kg/m^2 (n = 102,643) (%)
Age at enrollment (years)			
30–39	5.8	3.9	5.4
40–49	22.5	20.2	23.8
50–59	35.5	37.7	38.3
60–69	25.3	27.8	24.7
70–79	9.5	9.3	7.0
80–89	1.4	1.1	0.7
Sex			
Women	68.5	43.3	61.5
Men	31.5	56.7	38.5
Race			
White	94.8	92.6	89.4
Black	2.9	5.2	8.2
Other/unknown	2.3	2.2	2.3
Education			
Less than high school graduate	10.9	14.7	20.1
High school graduate	24.9	27.8	28.2
Some college	29.4	28.7	27.7
College graduate	17.9	14.6	11.7
Graduate school	15.7	12.9	10.8
Unknown	1.2	1.3	1.5
Diabetes	3.3	5.0	10.2
Cigarette smoking status[b]			
Never	43.8	47.7	49.9
Former	29.1	31.0	31.6
Current	27.1	21.2	18.5

[a]Percentages standardized to the age and sex distribution of the entire study population.
[b]Excludes never cigarette smokers who were current or former cigar/pipe smokers and former cigarette smokers who were current cigar/pipe smokers.

than that among never smokers ($P = 0.02$). Among former smokers, BMI HRs were elevated among those who had quit 20 or more years ago, but less clearly elevated among those who had quit less than 20 years ago. The BMI HR among former smokers who had quit less than 10 years ago was 1.24 (95% CI, 0.86–1.78). However, because there were small numbers in this category (51 cases), it was combined in **Table 3** with the much larger category of former smokers with 10 to <20 years since quit. There were no clear differences by cigarettes per day in the association of BMI with pancreatic cancer mortality among either former or current smokers when analyses were restricted to follow-up within 10 years of enrollment (Supplementary Table S1).

Discussion

In this prospective study of nearly a million men and women, higher BMI was associated with some increase in risk of pancreatic cancer mortality in each category of smoking status at enrollment (never, former, and current). However, associations with BMI appeared

Table 2. HRs per 5 units of BMI for pancreatic cancer mortality, by cigarette smoking status, CPS-II, 1985–2014.[a]

	Years since enrollment			
Smoking status at enrollment	**<10**	**10–<20**	**≥20**	**All follow-up years**
Never				
HR (95% CI)	1.22 (1.11–1.35)	1.22 (1.14–1.30)	1.21 (1.15–1.29)	1.22 (1.17–1.27)
Deaths/person-years	564/2,833,260	1,174/3,503,906	1,635/2,940,932	3,373/9,278,098
Former				
HR (95% CI)	1.03 (0.90–1.18)	1.22 (1.11–1.33)	1.22 (1.13–1.32)	1.18 (1.12–1.25)
Deaths/person-years	440/1,882,727	862/2,267,363	1,023/1,817,732	2,325/5,967,823
P value vs. HR in never smokers	0.04	0.94	0.90	0.43
Current				
HR (95% CI)	1.02 (0.90–1.16)	1.20 (1.10–1.31)	1.15 (1.06–1.26)	1.14 (1.07–1.20)
Deaths/person-years	501/1,455,176	802/1,703,317	903/1,312,657	2,206/4,471,150
P value vs. HR in never smokers	0.03	0.78	0.31	0.06

[a]All models adjusted for age, sex, race, and education. Models in former and current smokers additionally adjusted for cigarettes per day.

Table 3. HRs per 5 units of BMI for pancreatic cancer mortality by smoking status, cigarettes per day, and time since quit, CPS-II, 1985–2014.

	Deaths	Person-years	HR (95% CI) per 5 BMI units[a]	*P* value for different HR than among never smokers
Smoking status				
Never	3,373	9,278,098	1.22 (1.17–1.27)	—
Former, by years since quit[b]				
<20	357	1,248,411	1.08 (0.94–1.25)	0.12
20–<30	523	1,617,188	1.19 (1.06–1.33)	0.72
≥30	1,380	2,967,061	1.20 (1.12–1.29)	0.83
P trend[c]			0.32	
Former, by cigarettes per day				
<20	781	2,242,145	1.16 (1.06–1.27)	0.38
≥20	1,394	3,320,471	1.21 (1.13–1.30)	0.94
P trend[d]			0.11	
Current, by cigarettes per day				
<20	624	1,428,183	1.22 (1.10–1.35)	0.97
≥20	1,447	2,780,333	1.10 (1.03–1.18)	0.02
P trend[d]			0.06	

[a]All models adjusted for age, sex, race, and education. Models in former and current smokers additionally adjusted for cigarettes per day.
[b]Years since quit modeled as a time-dependent variable.
[c]*P* trend calculated using an interaction term between continuous BMI and continuous years since quit (time-dependent variable).
[d]*P* trend calculated using an interaction term between continuous BMI and continuous cigarettes per day.

weaker among current smokers, particularly current heavy smokers, and during follow-up within 10 years of enrollment, when current smokers at enrollment were the most likely to have still been smoking.

Our results are generally consistent with those of three previous prospective analyses that examined the association between BMI and pancreatic cancer incidence by never/former/current smoking status (10–12). **Table 4** summarizes results of these previous analyses together with our results. Taken together, evidence to date is consistent with a moderate association between BMI and pancreatic cancer risk among never and former smokers, but little or no association among current smokers. A pooled analysis of seven cohort studies published in 2010 (24) also reported stronger associations among never smokers and former smokers than among current smokers ($P = 0.08$ for interaction by smoking status). However, results of this pooled analysis are not shown in **Table 4** as data from most of the cohorts included were also included in one of the more recent analyses already shown in **Table 4**. Results from other cohort analyses, including a Swedish cohort (25), a pooled analysis of Japanese cohort studies (26), and a pooled analysis of African Americans in U.S. cohorts (27), also generally support the hypothesis that HRs for BMI are higher in never

Table 4. HRs for BMI and pancreatic cancer by smoking status from large cohort analyses.[a]

Study	Mean years of follow-up[b]	Comparison	HR and 95% CI by smoking status		
			Never	Former	Current
Million Women Study (10)					
HR (95% CI)[c]	7.2	BMI ≥25 vs. <25	1.14 (0.94–1.34)	1.38 (1.05–1.71)	1.06 (0.84–1.28)
Cases			516	323	421
Pooling Project (11)					
HR (95% CI)	11.6[d]	Per 5 BMI units	1.19 (1.08–1.31)	1.22 (1.10–1.34)	1.07 (0.95–1.21)
Cases			748	642	628
NIH-AARP cohort (12)					
HR (95% CI)	11.2	Per 5 BMI units	1.11 (1.05–1.17)	1.06 (0.99–1.14)	0.97 (0.89–1.05)
Cases			627	796	674
CPS-II (current report)					
HR (95% CI)	24.4	Per 5 BMI units	1.22 (1.17–1.27)	1.18 (1.12–1.25)	1.14 (1.07–1.20)
Cases			3,373	2,325	2,206
CPS-II, excluding follow-up >10 years after smoking report to reduce misclassification					
HR (95% CI)	9.7	Per 5 BMI units	1.22 (1.11–1.35)	1.03 (0.90–1.18)	1.02 (0.90–1.16)
Cases			564	440	501

[a]Table includes analyses of cohort studies including 500 or more cases and presenting results among never, former, and current smokers.
[b]Years from baseline to end of follow-up, including time within 1 year of baseline excluded from the NIH-AARP cohort analysis and time within 3 years of baseline excluded from the CPS-II analysis.
[c]CIs calculated from standard errors presented in this report.
[d]Estimated from information presented on number of participants and follow-up period for each cohort that contributed to this pooled analysis.

smokers. However, results from these analyses are difficult to compare with ours because they are not stratified by former and current smoking status.

Among former smokers in our analysis, the association between BMI and pancreatic cancer mortality (18% increase per 5 BMI units) appeared similar to that among never smokers (22% increase per 5 BMI units). However, during follow-up within 10 years of enrollment, the HR for BMI among former smokers was statistically significantly lower than that among never smokers. This result could be due at least partly to chance but could also be partly due to the higher proportion of more recent quitters among former smokers early in follow-up. BMI in recent quitters may sometimes reflect recent weight gain following smoking cessation, and recent weight gain may not have had a sufficient latency period to influence risk of pancreatic cancer. In analyses that examined BMI HRs among former smokers by years since quit, BMI was associated with statistically significantly higher risk only among those who had quit at least 20 years earlier, although there was not a statistically significant trend in BMI HRs by years since quit. Overall, evidence to date indicates that the association between BMI and pancreatic cancer is similar among never smokers and former smokers who quit 20 or more years ago. It remains unclear if this association is similar among never smokers and former smokers who quit less than 20 years ago.

There are at least three plausible reasons why the association between BMI and pancreatic cancer risk would be weaker in current smokers than in never smokers. First, the background rate of pancreatic cancer is higher among current smokers than among never smokers, so the same absolute increase in risk will result in a somewhat lower relative risk among current smokers than among never smokers. However, this explanation is not consistent with absence of any observable association between BMI and pancreatic cancer risk among current smokers in other large studies (10–12), or among current smokers within 10 years of enrollment in our study. Second, it is possible that the biological mechanisms through which excess weight increases pancreatic cancer risk are less important in smokers. For example, it is possible excess body weight does not contribute to hyperinsulinemia in some smokers because their ability to secrete insulin has been impaired by smoking-induced damage to the insulin-secreting cells of the pancreas (28). However, this explanation is speculative. Finally, among current smokers, associations with BMI may be attenuated by residual confounding by smoking given that smoking is generally associated with lower weight, driven by reductions in appetite and lean body mass (28). Although most epidemiologic analyses adjust for smoking characteristics, such as cigarettes per day, self-reported characteristics are unlikely to fully capture variation in exposure to tobacco smoke.

Results from analyses of waist circumference (WC) and pancreatic cancer may indirectly support the hypothesis that residual confounding by smoking weakens the association between BMI and pancreatic cancer among smokers. Although both BMI and WC are considered measures of adiposity, smoking is associated with lower BMI but not with lower WC (28). Therefore, among smokers, residual confounding by smoking is not likely to weaken associations between WC and pancreatic cancer the same way it may weaken associations with BMI. Indeed, in a large pooled analysis (29), the association between WC and pancreatic cancer did not differ by smoking status. This finding is consistent with the hypothesis that although adiposity increases risk of pancreatic cancer, residual confounding by smoking may be responsible for obscuring associations between BMI and pancreatic cancer among smokers.

It is important to note that even if smoking attenuates the true effect of excess weight on pancreatic cancer risk, rather than only the observed association, smoking is generally a stronger individual risk factor than excess weight. Therefore, quitting smoking will reduce an individual's overall risk of pancreatic cancer as well as risk of many other serious diseases.

Strengths of this analysis include its large size and prospective design. To our knowledge, this is the largest study to date to examine potential effect modification by smoking. Notably, the large size of this study allowed us to examine the association of BMI with pancreatic cancer by years since quit among former smokers and by cigarettes per day among current smokers. To our knowledge, this is the first study to examine associations with BMI by either years since quit or cigarettes per day. Although our results suggest that associations with BMI may be particularly attenuated among heavier smokers, this finding requires confirmation.

An important limitation of this analysis is the absence of updated information on smoking status. This is likely to have resulted in considerable misclassification of smoking status in later years of follow-up. The precise amount of smoking misclassification due to quitting smoking over time is unknown. However, a subcohort of about 184,000 CPS-II participants in 21 states agreed to complete a second questionnaire in 1992 or 1993 (30). In this subcohort, approximately 57% of participants who were current smokers in 1982 had quit by 1992 or 1993. Misclassification of current smokers who quit smoking during follow-up may have increased observed HRs for BMI among current smokers, making HRs for BMI in never and current smokers appear more similar. In addition, it should also be noted that our analysis examined pancreatic cancer mortality rather than pancreatic cancer incidence. However, our results are likely to be generalizable to pancreatic cancer incidence because pancreatic cancer is so highly fatal.

The observation that the association between BMI and pancreatic cancer risk is weaker among current smokers has implications for estimating the population burden of the disease. If excess body weight has a weaker effect on pancreatic carcinogenesis among current smokers, then currently available risk estimates for BMI from combined analyses of smokers and nonsmokers will overestimate risk among current smokers and underestimate risk among nonsmokers. However, if residual confounding by smoking is responsible for the weaker association between BMI and pancreatic cancer among current smokers, then currently available risk estimates will underestimate risk among everyone, including smokers, nonsmokers, and the population as a whole. It should be noted that there are additional reasons that currently available risk estimates for BMI may underestimate the risk associated with excess weight, including the measurement of BMI only relatively late in life (13–15). Fully understanding the impact of excess weight on the burden of pancreatic cancer risk is important given that pancreatic cancer rates are increasing in the United States despite declines in smoking (13–15).

Given the strong possibility of residual confounding by smoking, future analyses of BMI and pancreatic cancer risk should present BMI HRs specifically among never smokers or among never and long-term former smokers (e.g., quit 20 or more years ago) combined. These HRs could be validly generalized to populations with low prevalences of current smokers (e.g., older adults in the contemporary United States), and could also be validly used for risk prediction for individual nonsmokers. Alternatively, associations between WC and pancreatic cancer risk may be less attenuated by smoking. Therefore, population-attributable fractions calculated using risk estimates for WC might

provide a somewhat better estimate of the full impact of excess adiposity.

Our results support the hypothesis that the association between BMI and pancreatic cancer is weaker among current smokers than among never smokers. In populations where smoking prevalence is low, pancreatic cancer risk due to BMI is likely to be higher than that predicted by risk estimates from studies including substantial numbers of current smokers.

Disclosure of Potential Conflicts of Interest

W.D. Flanders reports that he owns Epidemiologic Research & Methods, LLC, which performs consulting work for clients. He knows of no conflicts with this work. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

E.J. Jacobs: Conceptualization, formal analysis, methodology, writing–original draft, writing–review and editing. **C.C. Newton:** Formal analysis, investigation, writing–review and editing. **V.L. Stevens:** Investigation, writing–review and editing. **A.V. Patel:** Investigation, writing–review and editing. **W.D. Flanders:** Investigation, writing–review and editing. **S.M. Gapstur:** Supervision, investigation, writing–review and editing.

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