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Published in:
Obesity (Silver Spring, Md.)

DOI:
10.1002/oby.23781

Publication date:
2023

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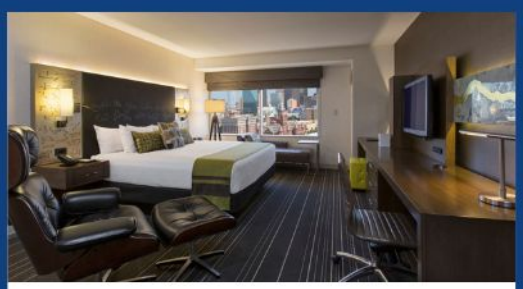

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Received: 25 October 2022 | Revised: 27 February 2023 | Accepted: 2 March 2023

DOI: 10.1002/oby.23781

ORIGINAL ARTICLE

Epidemiology/Genetics

Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

Fast-food environments and BMI changes in the Dutch adult general population: the Lifelines cohort

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Abstract

Objective: This study investigated cross-sectional and longitudinal associations of fast-food outlet exposure with BMI and BMI change, as well as moderation by age and genetic predisposition.

Methods: This study used Lifelines' baseline ($n = 141{,}973$) and 4-year follow-up ($n = 103{,}050$) data. Participant residential addresses were linked to a register with fast-food outlet locations (Nationwide Information System of Workplaces [Dutch: Landelijk Informatiesysteem van Arbeidsplaatsen, LISA]) using geocoding, and the number of fast-food outlets within 1 km was computed. BMI was measured objectively. A weighted BMI genetic risk score was computed, representing overall genetic predisposition toward elevated BMI, based on 941 single-nucleotide polymorphisms genome-wide significantly associated with BMI for a subsample with genetic data (BMI: $n = 44{,}996$; BMI change: $n = 36{,}684$). Multivariable multilevel linear regression analyses and exposure-moderator interactions were tested.

Results: Participants with ≥1 fast-food outlet within 1 km had a higher BMI (B [95% CI]: 0.17 [0.09 to 0.25]), and those with ≥2 fast-food outlets within 1 km increased more in BMI (B [95% CI]: 0.06 [0.02 to 0.09]) than participants with no fast-food outlets within 1 km. Effect sizes on baseline BMI were largest among young adults (age 18–29 years; B [95% CI]: 0.35 [0.10 to 0.59]) and especially young adults with a medium (B [95% CI]: 0.57 [−0.02 to 1.16]) or high genetic risk score (B [95% CI]: 0.46 [−0.24 to 1.16]).

Conclusions: Fast-food outlet exposure was identified as a potentially important determinant of BMI and BMI change. Young adults, especially those with a medium or high genetic predisposition, had a higher BMI when exposed to fast-food outlets.

INTRODUCTION

Overweight and obesity are major chronic disease risk factors [1]. Their combined worldwide adult prevalence has tripled from 13% in 1975 to 39% in 2016 [2], affecting more than 2 billion adults and contributing to rising health care costs [3]. Nevertheless, the complex and multifactorial etiology of overweight and obesity remains poorly understood.

Fast-food outlet exposure may be an important environmental determinant of overweight and obesity. Fast-food outlets typically offer cheap, highly caloric meals, are easily accessible, have long opening hours, and have increased substantially in number over the past decades [4]. A UK Biobank study found that people living within 500 m of the nearest fast-food outlet had a 0.10-kg/m^2 higher body mass index (BMI) than people living within 1000 to 1999 m of the nearest

fast-food outlet [5]. However, such evidence on the association between fast-food outlet exposure and BMI in adults could not be consistently replicated in other studies and it is predominantly based on cross-sectional data [6, 7]. For instance, a cross-sectional European-wide study on 5076 adults did not find associations between fast-food outlet exposure and self-reported BMI [8], and neither have such cross-sectional associations been found in the Health and Life Circumstances in Eindhoven and Surroundings (Dutch: Gezondheid en Levens Omstandigheden van de Bevolking van Eindhoven en omstreken [GLOBE]) study [9] and the European Prospective Investigation Into Cancer and Nutrition the Netherlands (EPIC-NL) cohort [10]. A scoping review of longitudinal studies on the association between fast-food outlet exposure and changes in BMI also yielded inconsistent results [11], which are mainly due to methodological limitations of the included studies (i.e., unrepresentative sample [12–14], misclassification due to use of neighborhood-level instead of individual-level exposure [15], potential confounding due to environmental factors, or reporting bias due to self-reported BMI) [16].

Young adulthood is a "sensitive" period to develop overweight or obesity because BMI increases relatively rapidly then [17]. Furthermore, young adults consume fast food relatively frequently [18]. Still, evidence on moderation by age in the association between fast-food outlet exposure and BMI is inconsistent [8, 19]. A longitudinal study on 115,260 US adults did not observe moderation by age in the association between residential fast-food outlet 5-km density and objectively measured BMI change over 5 years [14]. Still, moderation effects may have been underestimated because of the relatively wide 5-km density measure and use of large age categories (i.e., 18–44 or 45–64 years). Another US study ($n = 679$) also found no moderation by age in the association between fast-food outlets within 1.6 km and objectively measured 2-year BMI change [20]. Here, moderation effects may have been underestimated because of the small sample size and relatively short follow-up.

Besides young adults, individuals with a high genetic predisposition toward elevated BMI may also be disproportionally affected by fast-food outlets. Such individuals tend to have a relatively weak sense of satiety after eating, frequently eat in the absence of hunger, have a large appetite, and are more likely to engage in emotional eating [21]. To represent overall genetic predisposition toward elevated BMI and aggregate the effects of common identified genetic variants (single-nucleotide polymorphisms [SNPs]) linked with BMI, a genetic risk score (GRS) can be calculated. Recent genome-wide association studies (GWASs) have identified many genetic variants (SNPs) for BMI. These SNPs only have small individual effects on BMI, but, when aggregated into a GRS, the effects of these SNPs together can be substantial [22]. However, studies on moderation by a GRS in the association between fast-food outlet exposure and BMI are scarce because this requires complex linkages among participant health data, residential addresses, fast-food outlet locations, and genetic data. Such linkages are expensive, computationally challenging, and rarely available worldwide. Two studies conducted in the UK have investigated moderation by a GRS in the association between fast-food outlet exposure and BMI. A study using data from the UK Biobank found stronger associations among individuals with a higher GRS [23], but data from the UK Fenland Study did not confirm this finding [24]. These two studies used a GRS based on, respectively, 91 and 96 SNPs genome-wide significantly associated with BMI. More recently, 941 genome-wide significant SNPs have been identified for BMI [25], allowing for a GRS that more accurately represents genetic predisposition. Furthermore, these studies used cross-sectional data and they did not include certain other environmental determinants (e.g., healthy food outlets).

Ultimately, more rigorous investigations on the associations of fast-food outlet exposure with BMI and BMI change and the moderating roles of age and genetic predisposition herein are needed based on objective fast-food outlet exposure and BMI (change) data in a cohort representative of the general population. Such investigations may improve our understanding of why certain people develop an elevated BMI and elucidate the roles of fast-food outlet exposure and genetic factors over the life course herein. We investigated the cross-sectional and longitudinal associations of residential fast-food outlet exposure with BMI and ±4-year changes in BMI in the adult general population. We also investigated to what extent these cross-sectional and longitudinal associations were moderated by age and a BMI GRS

Study Importance

What is already known?

- Evidence on the associations of fast-food outlet exposure with BMI and changes in BMI is inconsistent. Most studies have used cross-sectional data and nonrepresentative samples of the general population. Furthermore, it is unclear to what extent fast-food outlet exposure interacts with genetic factors over the life course.

What does this study add?

- We identified fast-food outlet exposure as a potentially important determinant of BMI and changes in BMI in a large-scale cohort representative of the general population of the northern Netherlands.
- Young adults and especially young adults with a medium or high genetic predisposition had a higher BMI when exposed to fast-food outlets.

How might these results change the direction of research?

- Policy approaches aimed at reducing BMI should target not only individuals but also the fast-food environments that these individuals live in.
- This study may be a starting point for researchers to identify how fast-food outlet exposure interacts with genetic factors on BMI over the life course.

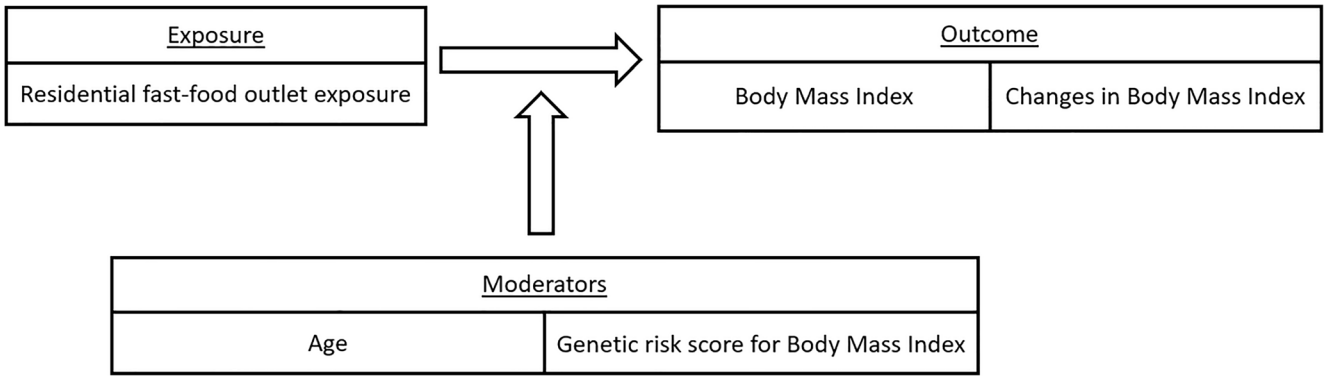

FIGURE 1 Illustration of the moderation model under study

based on 941 SNPs genome-wide significantly associated with BMI (Figure 1). We hypothesized that individuals with higher fast-food outlet exposure have a higher BMI and experience greater increases in BMI over ±4 years and that these patterns are stronger among younger adults, adults with a higher GRS, and especially younger adults with a higher GRS.

METHODS

Study population

We used adult data from the baseline (December 2006 to December 2013) and first follow-up assessment (January 2014 to December 2017) of Lifelines, a multidisciplinary, prospective, population-based cohort study. Participants were recruited through general practitioners, participants' family members, and online registrations. Lifelines is broadly representative of the adult general population of the northern Netherlands regarding socioeconomic factors, lifestyle, chronic diseases, and general health [26]. Using nationwide address registry data, participants' residential addresses were obtained and geocoded.

For this study, we excluded participants residing in a nursing home at some point between baseline and follow-up assessment because they may not have been able to interact with their fast-food environment ($n = 324$); women who were pregnant at or in the year prior to the assessment whose BMI measurement may not represent their actual weight status ($n = 4{,}888$); and participants with missing data on fast-food outlet exposure or BMI or >30% missing data points on covariates and potential confounders ($n = 3{,}105$). For BMI change analyses, we additionally excluded participants lost to follow-up ($n = 38{,}923$).

Data linkage

We linked participants' geocoded residential addresses at baseline to LISA (www.lisa.nl), a Dutch register containing locations where paid work is performed for ≥1 h/mo. In line with previous research [27], residential addresses were linked to 2012 LISA data, corresponding with the median recruitment year of the baseline assessment. Using this linkage, we extracted locations of fast-food outlets, healthy food outlets, and physical activity facilities (Supporting Information Table S1) [27]. In addition, Lifelines participants' 2012 residential neighborhood code was linked to 2012 Statistics Netherlands neighborhood data [28]. Neighborhood boundaries were based on official Statistics Netherlands administrative definitions. Dutch neighborhoods cover a median (interquartile range [IQR]) surface of 84 (35–289) hectares and contain a median (IQR) of 660 (180–1850) residents.

Exposure

Based on the LISA linkage, we computed the number of fast-food outlets within a straight-line distance of 1 km of the residential address at baseline. The 1-km distance was based on previous research in the Dutch setting that found stronger associations with BMI than fast-food outlet exposure within 500 m, 3 km, and 5 km [29]. Because the number of fast-food outlets within 1 km was nonlinearly associated with (changes in) BMI in our data, we categorized this variable as null (reference group), one, or at least two.

Outcome

BMI at baseline and change in BMI between baseline and follow-up assessment were the outcomes. BMI was based on objective weight (without shoes and heavy clothing), and height measurements taken by trained research staff.

Moderators

Age at baseline was categorized into 18 to 29, 30 to 39, 40 to 49, 50 to 59, and 60+ years. Age of 60+ years was taken as one single category because adults aged 60 to 69 years and adults aged 70+ years decrease similarly in BMI [30] and because it resulted in a substantial number of participants to ensure sufficient power in the

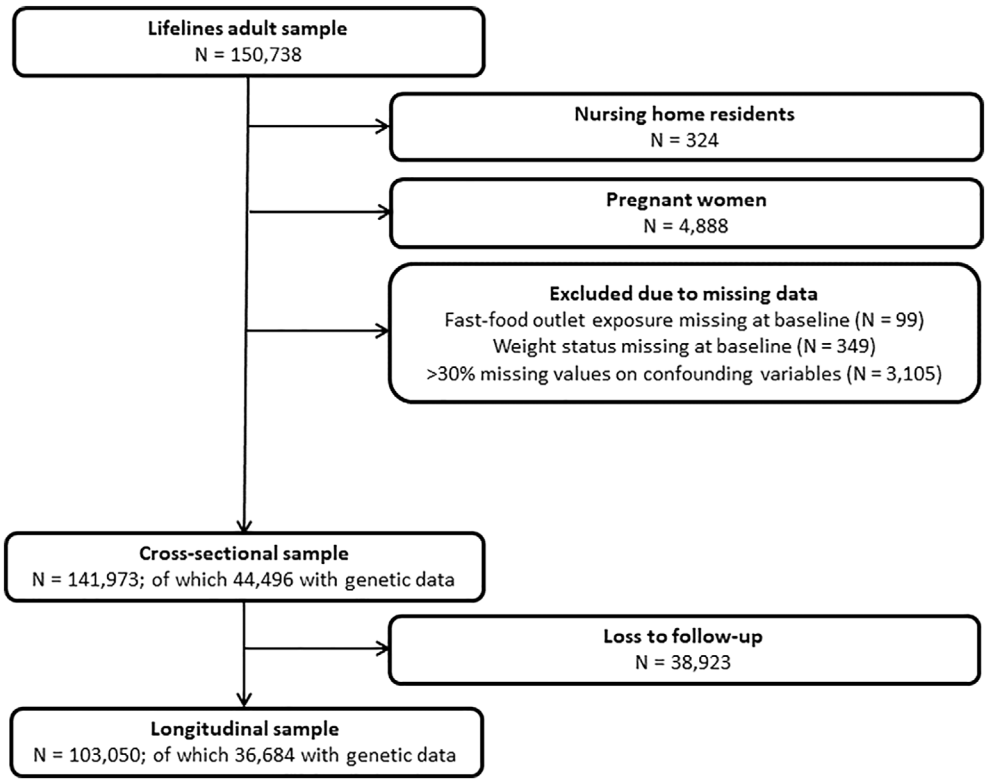

FIGURE 2 Flowchart describing the inclusion of participants in the current study

statistical analysis. We computed a weighted BMI GRS for a subsample of participants with available genetic data ($n = 44,496$ for the analyses on BMI and $n = 36,684$ for the analyses on changes in BMI). This BMI GRS represents overall genetic risk toward elevated BMI via various pathways, including eating behaviors [21]. First, we selected a list of 941 SNPs that were genome-wide significantly associated with BMI from a 2018 meta-analysis of GWASs for BMI in ~700,000 individuals of European ancestry [25], and we also obtained effect sizes for each of these 941 SNPs on BMI. Second, we extracted the dosage of these 941 SNPs from Lifelines' genotyped and imputed data. Participants' DNA samples were genotyped using the Illumina Global Screening Array and Illumina CytoSNP12v2 array. After quality control, both genotyped data sets were imputed at the Sanger imputation server using Haplotype Reference Consortium panel r1.1 [31]. Finally, we calculated the weighted GRS by summing risk allele dosages of 941 SNPs weighted by the corresponding effect sizes. We divided the GRS into tertiles (low, medium, and high).

Covariates and potential confounders

Individual-level covariates and potential confounders at baseline were as follows: sex; weekly working hours (0, 1–11, 12–19, 20–31, or ≥32); household size (living alone or together); number of healthy food outlets within 1 km; number of physical activity facilities within 1 km; net income (treated continuously using the middle value of categories <€750 [set to €500], €750–€1000, subsequent €500-intervals until €3500, and >€3500 [set to €3750], divided by the square root of individuals living from that income); and highest level of completed education (low, middle, or high based on the International Standard Classification of Education) [32]. Neighborhood-level covariates and potential confounders were based on linkage with Statistics Netherlands and they included address density (addresses per kilometer squared) and neighborhood socioeconomic status. Neighborhood socioeconomic status was measured as a standardized composite score through principal component analysis, based on the following: the average value of a house; percentage owner-occupied houses; mean net monthly income; and percentage individuals aged 15 to 65 years not receiving assistance benefits.

Statistical analysis

After applying the exclusion criteria, we imputed missing data using multiple imputation by chained equations and created 10 imputed data sets (Supporting Information Table S8). We performed multiple imputation because the pattern of missingness was likely missing at random, considering that missingness on certain variables was likely related to other variables (e.g., low-educated individuals may be more likely not to report income). Subsequently, we used multivariable multilevel linear regression models to examine associations between fast-food outlet exposure and (changes in) BMI. We accounted for clustered data within neighborhoods using random slopes and random intercepts [33] because we theorized that both intercepts and slopes

TABLE 1 Baseline characteristics of study population for cross-sectional analyses and longitudinal analyses and for the subsets of participants with genetic data available for these analyses

	Cross-sectional analyses		Longitudinal analyses	
	Study population ($n = 141,973$)	Study population with genetic data available ($n = 44,496$)	Study population ($n = 103,050$)	Study population with genetic data available ($n = 36,684$)
Age (y), mean (SD)	44.6 (12.6)	44.7 (13.3)	45.8 (12.3)	45.6 (12.9)
Sex, *n* (%)				
Female	81,154 (57.2)	25,530 (57.4)	58,582 (56.8)	21,018 (57.3)
Male	60,819 (42.8)	18,966 (42.6)	44,468 (43.2)	15,666 (42.7)
Weekly working hours, mean (SD)	21.6 (18.5)	19.5 (18.3)	21.5 (18.3)	19.6 (18.2)
Highest level of completed education, *n* (%)				
Low	42,308 (30.2)	13,168 (29.9)	29,909 (29.3)	10,767 (29.7)
Middle	56,295 (40.1)	17,865 (40.6)	40,521 (39.8)	14,569 (40.2)
High	41,701 (29.7)	12,980 (29.5)	31,505 (30.9)	10,946 (30.2)
Household situation, *n* (%)				
Living alone	15,251 (10.8)	4,363 (9.8)	10,771 (10.5)	3,516 (9.6)
Living together	126,491 (89.2)	401,33 (90.2)	92,279 (89.5)	33,168 (90.4)
Income, mean (SD)	1,529 (580)	1,506 (579)	1,554 (574)	1,528 (573)
BMI, mean (SD)	26.1 (4.3)	25.9 (4.2)	26.0 (4.2)	25.9 (4.1)
WHtR, mean (SD)	0.52 (0.07)	0.51 (0.07)	0.52 (0.07)	0.51 (0.07)
GRS of BMI, mean (SD)	0.10 (0.32)	0.10 (0.32)	0.10 (0.32)	0.10 (0.32)
Number of fast-food outlets within 1 km, median (IQR)	3 (1–8)	3 (1–7)	3 (1–7)	3 (1–7)
Number of physical activity facilities within 1 km, median (IQR)	1 (0–3)	1 (0–3)	1 (0–3)	1 (0–3)
Number of healthy food outlets within 1 km, median (IQR)	2 (1–5)	2 (1–5)	2 (1–4)	2 (1–5)
Neighborhood address density, median (IQR)	605 (204–1,135)	620 (199–1,117)	595 (198–1,129)	616 (194–1,096)
Neighborhood socioeconomic status, mean (SD)	0.00 (1.00)	0.02 (0.99)	0.02 (1.00)	0.05 (0.97)
Follow-up time (y), mean (SD)	3.9 (1.2)	4.1 (1.2)	3.9 (1.2)	4.1 (1.2)

Note: Baseline characteristics are based on nonimputed data.
Abbreviations: GRS, genetic risk score; WHtR, waist to height ratio.

would differ across neighborhoods. Assumptions of the multilevel linear regression models [33] were met. We adjusted for the covariates and potential confounders. For analyses on BMI change, we additionally adjusted for baseline BMI and follow-up time (in years). We presented effect sizes on unstandardized BMI with B representing unit increases per kilograms per meter squared (kg/m^2). We also presented 95% confidence intervals (CI) and used $\alpha = 0.05$ for statistical significance.

To assess moderation by age and GRS, we assessed two-way interactions between fast-food outlet exposure and age; two-way interactions between fast-food outlet exposure and GRS; and three-way interactions among fast-food outlet exposure, age, and GRS. If the p value of one of these interaction terms was <0.10, we conducted stratified analyses. The cutoff for $p < 0.10$ was chosen because we expected effect sizes of interactions to be smaller than main effects, resulting in lower power [34]. In moderation analyses by GRS, we additionally adjusted for genotyping array and four genetic principal components to address genetic population stratification [35].

To evaluate the robustness of results, we conducted two sensitivity analyses. First, analyses were repeated for the outcome waist to height ratio (WHtR) instead of using BMI. BMI is commonly used because of its quick and inexpensive measurement but it does not adequately reflect fat mass and regional fat distribution, thereby introducing misclassification. WHtR more accurately measures fat mass and it is less susceptible to misclassification than BMI [36]. Second, we repeated the analyses on BMI change without participants who moved houses between baseline and follow-up ($n = 86,730$). Third, we repeated the analyses on obesity prevalence and incidence using multilevel logistic regression models because obesity is more relevant than BMI from a clinical perspective.

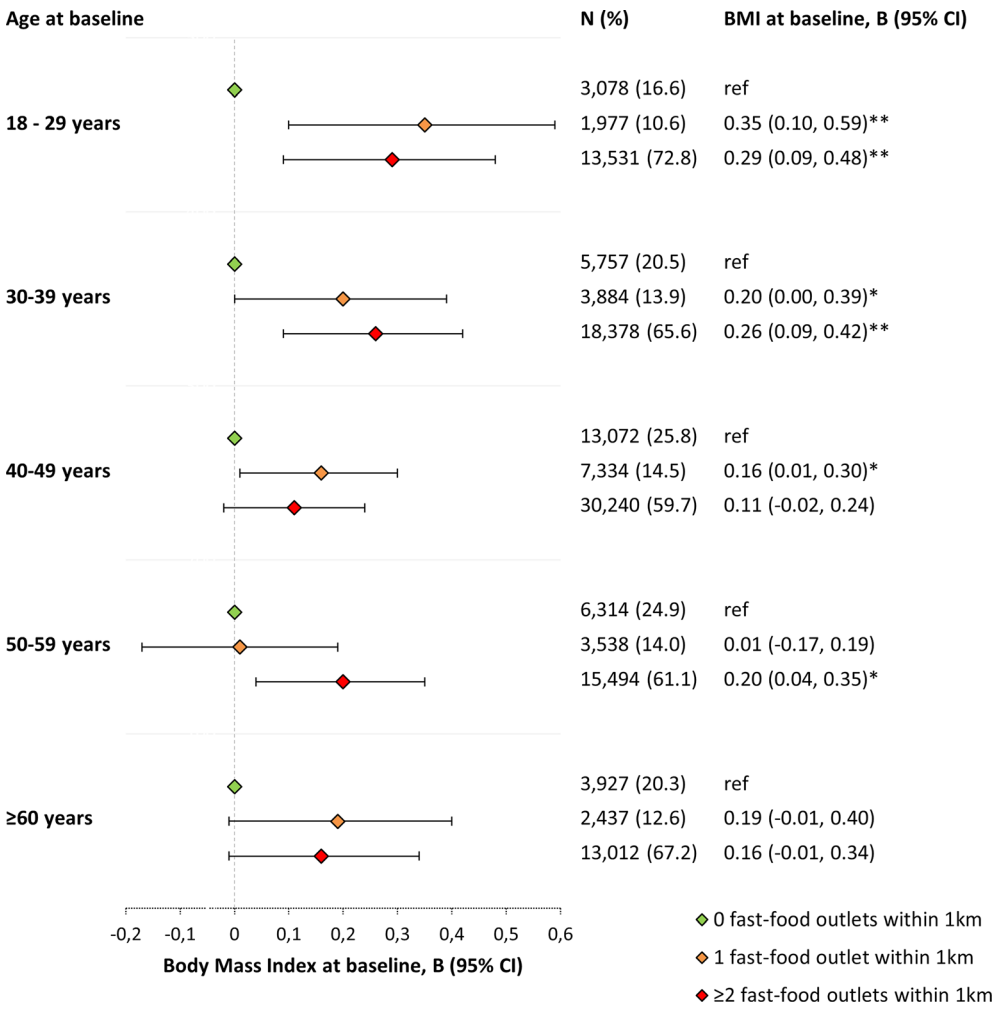

FIGURE 3 Multilevel analyses on the association between fast-food outlet exposure and BMI at baseline, separately for participants aged 18 to 29, 30 to 39, 40 to 49, 50 to 59, and 60+ years. Analyses were adjusted for sex, weekly working hours, highest level of completed education, household situation, income, number of physical activity facilities within 1 km, number of healthy food outlets within 1 km, neighborhood address density, and neighborhood socioeconomic status. *$p < 0.05$; **$p < 0.01$

Ethics approval

The Lifelines Cohort Study complies with the Declaration of Helsinki. The local medical ethics committee approved the protocol (1007/152). Informed consent was provided by all participants.

RESULTS

At baseline, the 141,973 eligible participants (Figure 2) had a mean age of 44.6 (standard deviation [SD]: 12.6) years, and 57.2% were female (Table 1). The mean BMI at baseline was 26.1 (SD: 4.3) kg/m^2. The median number of fast-food outlets was 3 (IQR: 1–7). The mean BMI for adults aged 18 to 29, 30 to 39, 40 to 49, 50 to 59, and 60+ years was 24.1 (SD: 4.0), 25.7 (SD: 4.3), 26.4 (SD: 4.4), 26.5 (SD: 4.1), and 27.0 (SD: 3.9) kg/m^2, respectively. The subsample of 44,496 participants with genetic data was similar to the 141,973 eligible participants at baseline in terms of fast-food outlet exposure, BMI, and sociodemographic characteristics (Table 1). The mean baseline BMI for participants with a low, medium, or high GRS was 24.9 (SD: 3.8), 25.8 (SD: 4.0), and 26.9 (SD: 4.5) kg/m^2, respectively. The GRS explained 4.8% of the variance of baseline BMI.

The mean follow-up time for the 103,050 eligible participants who attended the follow-up visit was 3.9 (SD: 1.2) years, and the mean BMI change was 0.15 (SD: 1.75) kg/m^2. Compared with participants who attended the follow-up visit, participants lost to follow-up had a higher baseline BMI, were younger, and more often reported a low educational level (Supporting Information Table S2).

Association between fast-food outlet exposure and BMI

The cross-sectional multilevel models taking clustered data within neighborhoods into account showed that participants with one or at least two fast-food outlets within 1 km of the residential

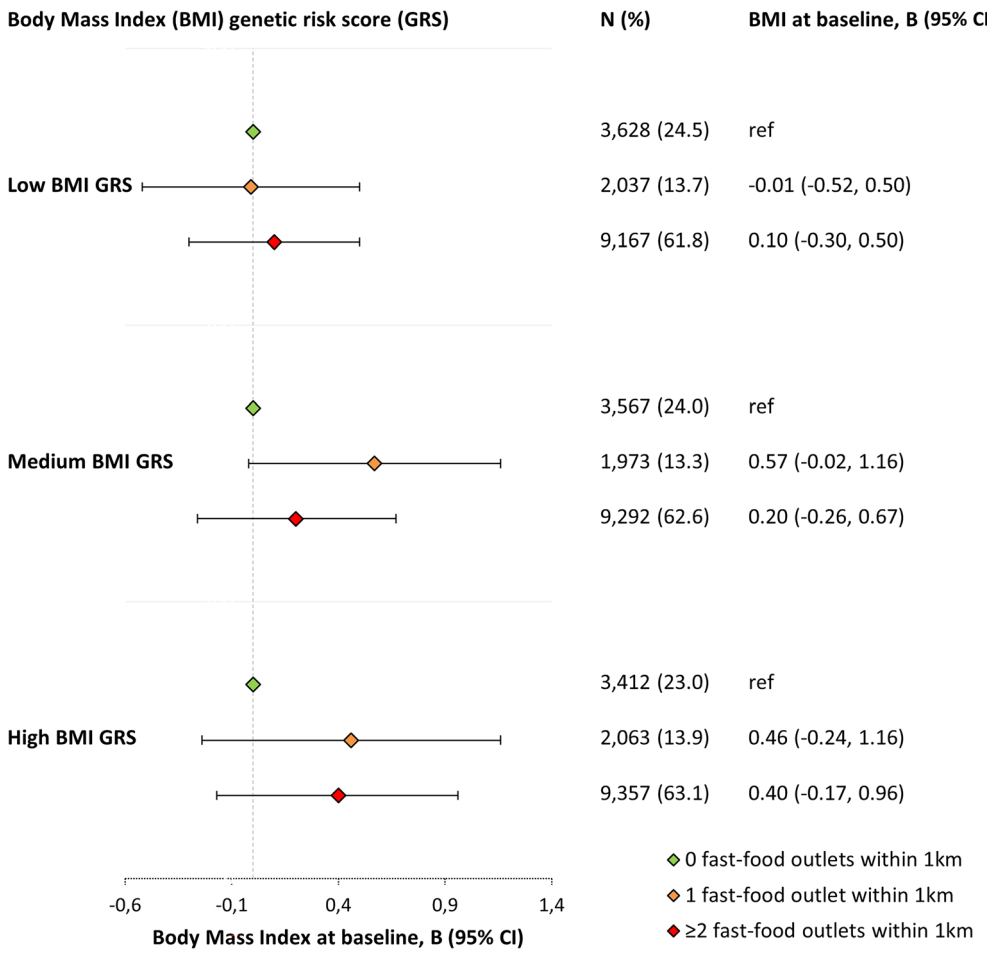

FIGURE 4 Multilevel analyses on the association between fast-food outlet exposure and BMI at baseline for participants aged 18 to 29 years, stratified according to BMI genetic risk score (low, medium, or high). Analyses were adjusted for sex, weekly working hours, highest level of completed education, household situation, income, number of physical activity facilities within 1 km, number of healthy food outlets within 1 km, neighborhood address density, neighborhood socioeconomic status, genotyping array (Illumina Global Screening or Illumina CytoSNP12v2 array), and four genetic principal components to account for genetic population stratification.

address had a higher BMI than participants with no fast-food outlet within the same radius (B [95% CI]: 0.17 [0.07 to 0.26] kg/m^2 and 0.17 [0.09 to 0.25] kg/m^2, respectively; Supporting Information Table S3). The *p* values of the interaction terms among fast-food outlet exposure and age (two-way interaction); fast-food outlet exposure and GRS (two-way interaction); and fast-food outlet exposure, age, and GRS (three-way interaction) on BMI were 0.08, 0.24, and 0.09, respectively. Therefore, stratified analyses by age and by both age and GRS were performed. Stratified analyses by age showed significant associations between fast-food outlet exposure and BMI for participants under 60 years old, with the largest effect sizes in adults aged 18 to 29 years (B [95% CI]: 0.35 [0.10 to 0.59] kg/m^2; Figure 3). Stratified analyses by both age and GRS showed relatively large but nonsignificant effect sizes of fast-food outlet exposure on BMI among young adults (age 18–29 years) with a medium GRS (B [95% CI]: 0.57 [−0.02 to 1.16] kg/m^2) and a high GRS (B [95% CI]: 0.46 [−0.24 to 1.16] kg/m^2) compared with young adults with a low GRS (B [95% CI]: −0.01 [−0.52 to 0.50] kg/m^2; Figure 4, Supporting Information Table S4).

Association between fast-food outlet exposure and changes in BMI

Participants with at least two fast-food outlets within 1 km of the residential address increased more in BMI over ±4 years than participants with no fast-food outlet within the same radius (B [95% CI]: 0.06 [0.02 to 0.09] kg/m^2; Supporting Information Table S3). *P* values of the interaction terms between fast-food outlet exposure and age (two-way interaction); fast-food outlet exposure and GRS (two-way interaction); and fast-food outlet exposure, age, and GRS (three-way interaction) on BMI change were <0.01, 0.36, and 0.02, respectively. Therefore, stratified analyses by age and by both age and GRS were performed. In stratified analyses by age, we observed only slightly larger effect sizes for fast-food outlet exposure on ±4-year changes in BMI in adults aged 40 to 49 and 50 to 59 years compared with other age groups (Figure 5; B [95% CI]: 0.07 [0.01 to 0.12] kg/m^2 and 0.07 [0.00 to 0.15] kg/m^2 for adults aged 40–49 and 50–59 years, respectively). In stratified analyses by age and GRS, a clear moderation pattern by age and GRS was lacking, and

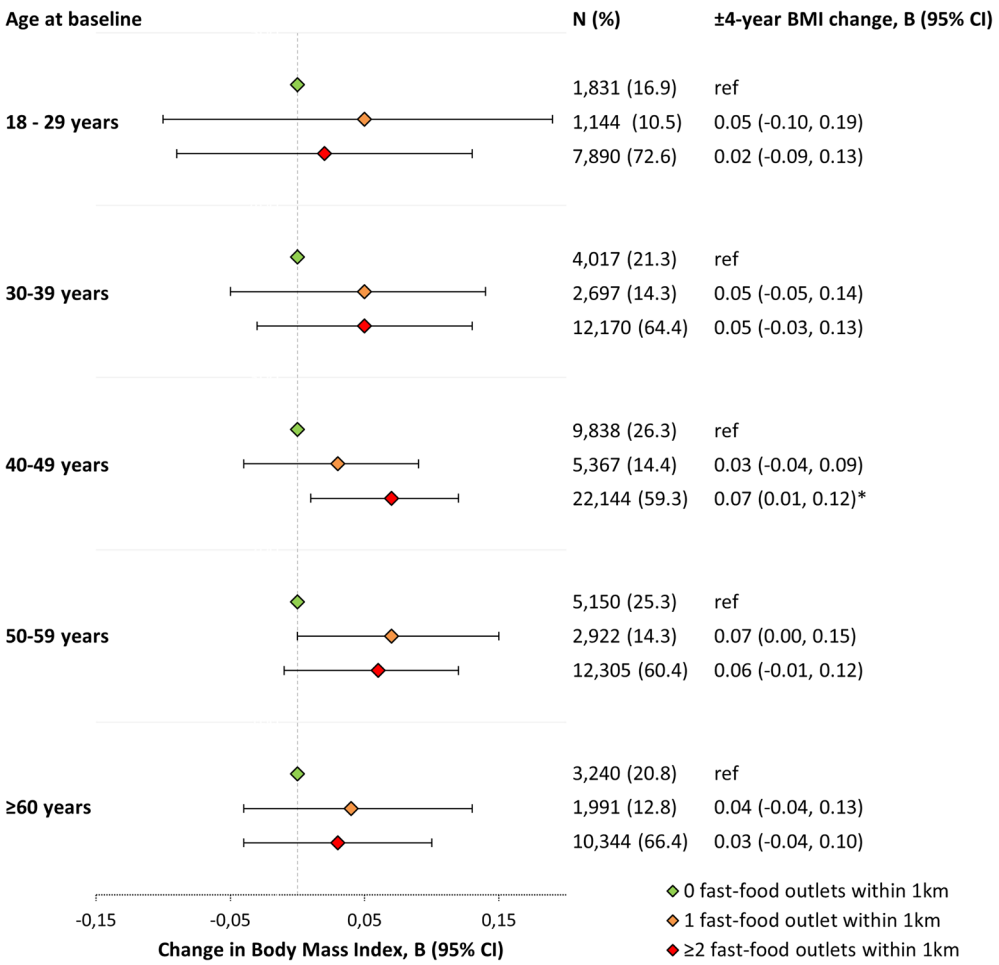

FIGURE 5 Multilevel analyses on the association between fast-food outlet exposure and changes in BMI over ±4 years, separately for participants aged 18 to 29, 30 to 39, 40 to 49, 50 to 59, and 60+ years. Analyses were adjusted for BMI at baseline, sex, weekly working hours, highest level of completed education, household situation, income, number of physical activity facilities within 1 km, number of healthy food outlets within 1 km, neighborhood address density, neighborhood socioeconomic status, and follow-up time. *$p < 0.05$

fast-food outlet exposure was not associated with BMI changes in any of the strata (Table 2).

Sensitivity analyses

Results did not change when repeating the analyses with WHtR instead of BMI as the outcome (Supporting Information Table S5) or with only participants who did not move houses between baseline and follow-up ($n = 86{,}730$; Supporting Information Table S6). Results of the analyses on obesity as the outcome were similar to results of analyses on BMI as the outcome, except that individuals with a high GRS had an increased risk of developing obesity when being exposed to at least two fast-food outlets within 1 km (odds ratio [OR] [95% CI]: 1.46 [1.09 to 1.96]; Supporting Information Table S7).

DISCUSSION

This study shows that individuals with at least one fast-food outlet within 1 km from their residential address had a higher BMI. The association between fast-food outlet exposure and BMI was stronger among young adults (age 18–29 years) and especially young adults with a medium or high GRS. Furthermore, individuals with at least two fast-food outlets within 1 km increased more in BMI during the ±4-year follow-up than individuals who had no fast-food outlet within the same radius. Associations between fast-food outlet exposure and changes in BMI were slightly larger in individuals aged 40 to 49 years. We found effect sizes of fast-food outlet exposure on BMI change up to 0.06 kg/m^2. This equals a 0.20-kg and 0.17-kg higher weight for Dutch male and Dutch female individuals with average height, respectively (i.e., 1.81 m and 1.68 m, respectively) [37]. This effect size is small on an individual level. However, on a population level, the role of fast-food outlet exposure may be greater. As a large proportion of the population is exposed to fast-food outlets, this exposure could potentially result in a small shift in population mean BMI, subsequently resulting in substantial increases in overweight and obesity [38].

As hypothesized, multilevel models addressing clustered data within neighborhoods showed that individuals with higher fast-food outlet exposure had a higher BMI and experienced a greater change in BMI over ±4 years. High levels of fast-food outlet exposure may

TABLE 2 Multilevel analyses on the association between fast-food outlet exposure and changes in BMI, stratified according to BMI GRS and stratified according to age and BMI GRS

	Number of fast-food outlets within 1 km		
	0 Fast-food outlets within 1 km	1 Fast-food outlet within 1 km	≥2 Fast-food outlets within 1 km
Subgroup of participants		Change in BMI (kg/m^2), B (95% CI)[a]	Change in BMI (kg/m^2), B (95% CI)[a]
Subgroups of BMI GRS			
Low GRS	ref	0.05 (−0.04 to 0.14)	−0.01 (−0.08 to 0.07)
Medium GRS	ref	0.03 (−0.08 to 0.13)	0.09 (0.00 to 0.18)
High GRS	ref	0.04 (−0.07 to 0.16)	0.05 (−0.05 to 0.15)
Subgroups of age (y) and BMI GRS			
18–29 and low BMI GRS	ref	−0.04 (−0.35 to 0.27)	0.11 (−0.13 to 0.35)
18–29 and medium BMI GRS	ref	−0.10 (−0.47 to 0.27)	0.00 (−0.29 to 0.29)
18–29 and high BMI GRS	ref	0.06 (−0.34 to 0.46)	−0.10 (−0.43 to 0.22)
30–39 and low BMI GRS	ref	0.05 (−0.19 to 0.30)	−0.06 (−0.27 to 0.14)
30–39 and medium BMI GRS	ref	0.04 (−0.02 to 0.10)	0.05 (−0.01 to 0.10)
30–39 and high BMI GRS	ref	0.14 (−0.15 to 0.43)	0.14 (−0.11 to 0.38)
40–49 and low BMI GRS	ref	0.03 (−0.13 to 0.19)	−0.02 (−0.15 to 0.11)
40–49 and medium BMI GRS	ref	−0.02 (−0.21 to 0.16)	0.09 (−0.06 to 0.24)
40–49 and high BMI GRS	ref	−0.02 (−0.21 to 0.18)	0.06 (−0.11 to 0.23)
50–59 and low BMI GRS	ref	0.04 (−0.13 to 0.22)	0.02 (−0.13 to 0.17)
50–59 and medium BMI GRS	ref	0.11 (−0.10 to 0.31)	0.07 (−0.10 to 0.25)
50–59 and high BMI GRS	ref	0.07 (−0.15 to 0.28)	0.05 (−0.14 to 0.24)
60+ and low BMI GRS	ref	0.11 (−0.12 to 0.33)	−0.02 (−0.20 to 0.16)
60+ and medium BMI GRS	ref	0.01 (−0.20 to 0.23)	0.08 (−0.11 to 0.26)
60+ and high BMI GRS	ref	0.13 (−0.13 to 0.39)	0.03 (−0.19 to 0.24)

Abbreviation: GRS, genetic risk score; ref, reference.

[a]With multivariable adjustment for age, sex, weekly working hours, highest level of completed education, household situation, income, number of physical activity facilities within 1 km, number of healthy food outlets within 1 km, neighborhood address density, neighborhood socioeconomic status, whether participants were genotyped using the Illumina Global Screening Array or Illumina CytoSNP12v2 array, four genetic principal components to account for genetic population stratification, BMI at baseline, and follow-up time.

lower the barrier for fast-food consumption, and fast-food consumption has been consistently linked with weight gain [39]. Interestingly, a Dutch cross-sectional study on the EPIC-NL cohort ($n = 8231$) did not find an association between fast-food outlet exposure and BMI-based overweight and obesity [10], but associations in this study may have been underestimated by the use of self-reported BMI. Another Dutch cross-sectional study even found that individuals with higher fast-food outlet exposure had a lower BMI [9], perhaps because of differential adjustment for neighborhood-level variables (e.g., address density). Contrary to longitudinal studies in the US and Sweden [12, 13, 15, 40], we found an association between fast-food outlet exposure and BMI change. Between-country differences in the structure of the built environment, dietary habits, and eating culture may explain this discrepancy. In addition, differences regarding study populations, exposure measurement, and use of self-reported BMI could explain the contradicting findings. To overcome this methodological heterogeneity, large-scale, representative cohorts with standardized objective measurements should be available for researchers. To this end, the Geoscience and Health Cohort Consortium and Canadian Urban Environmental Health Research Consortium [41] created a centralized repository with multiple such cohorts, stimulating rigorous future fast-food environment research.

Partly in line with our hypothesis, the cross-sectional, but not the longitudinal, association between fast-food outlet exposure and BMI was stronger in young adulthood (18–29 years) than in midlife or older age. A potential explanation for the results of cross-sectional analyses is that young adults consume fast food relatively frequently [18]. This finding was not confirmed in longitudinal analyses: effect sizes of fast-food outlet exposure on changes in BMI were largest in midlife, even though these effect sizes only differed little across age groups. Our stronger associations with BMI change for midlife individuals conflict with two studies from the US that found no moderation by age in the association between fast-food outlet exposure and BMI change [14, 20]. This difference may be explained by our large sample size and use of relatively specific age categories (i.e., one of those studies categorized age as 18–44 and 45–64 years, whereas we used 10-year intervals) [14]. A potential explanation for the stronger association between fast-food outlet and BMI change in midlife may be that such individuals spend more time and consume unhealthy foods more often in their residential neighborhood (rather than at families' or

friends' places) than young adults [42]. In addition, metabolism slows down with age [43], possibly resulting in a higher impact of fast-food consumption on BMI in midlife than in young adulthood. This slower metabolism may make midlife individuals relatively susceptible to residential fast-food outlet exposure.

Partly in line with our hypothesis, the association between fast-food outlet exposure and BMI, but not BMI change, was stronger in young adults with a medium or high GRS. Individuals with a high GRS were at greater risk of incident obesity when exposed to fast-food outlets. Interestingly, this moderating role of the GRS in the association between fast-food outlet exposure and BMI was found only in young adults, perhaps because especially young adults with a medium or high GRS engage in unhealthy diets such as fast-food consumption. Another explanation is that the GRS exerts its effects in young adulthood rather than later life stages. However, the moderation pattern by age and GRS was not corroborated in longitudinal analyses, possibly because the GRS effects were already manifested in childhood [22] and because there was less variability in BMI change than in baseline BMI. In addition, the GRS was calculated based on a cross-sectional BMI GWAS rather than a longitudinal BMI GWAS because no GWAS results are available for changes in BMI. Consequently, potential moderation effects of the GRS may have been underestimated in longitudinal analyses.

Strengths of this study include the longitudinal design and the large-scale sample representative of the northern Netherlands general population [26], ensuring generalizability of findings. Furthermore, the objective BMI measurement and calculation of the GRS using 941 SNPs from the most recent GWAS of BMI [25] reduce the risk of information bias. A limitation of this study is the risk of attrition bias due to loss to follow-up in the longitudinal analyses. This could have resulted in underestimated associations because participants who did not attend the follow-up visit had a higher BMI than those who did. Besides, we had data available for residential fast-food outlet exposure based only on straight-line distances rather than street-network distances. Street-network distances may more accurately measure fast-food outlet exposure than straight-line distances in areas with a lower street connectivity. Also, fast-food outlets within 1 km may imperfectly measure fast-food outlet exposure because individuals may spend time in other areas than this 1-km density. However, fast-food outlet exposure within 1 km is more closely associated with BMI than fast-food outlet exposure within other ranges (e.g., 500 m, 3 km, 5 km) [29]. Results may further have been affected by temporal mismatch between measurement of fast-food exposure (2012) and baseline BMI (2006 to 2013). Still, 85.2% of participants were recruited between 2010 and 2013, and previous research in Lifelines has shown that the impact of this temporal mismatch is limited [27]. Furthermore, the follow-up period of approximately 4 years was relatively short to assess associations between fast-food environments and BMI change. Finally, 16% of participants did not report their income in this study.

A key implication of this study is that policies aimed at reducing BMI should target not only individuals but also their fast-food environments. An example of such a policy is the regulating of fast-food environments through urban planning. Fast-food marketing restrictions have also been proposed to reduce fast-food consumption. Restrictions on junk food marketing in the London, England, transport system resulted in a 4.8% lower obesity prevalence in London [44]. Future studies should evaluate these policy changes through before-after evaluations. In addition, studies with follow-up periods >4 years are needed to investigate the association between fast-food outlets and BMI change. Finally, more studies should be conducted on gene and fast-food environment interactions.

CONCLUSION

Our findings identify fast-food outlet exposure as a potentially important determinant of BMI (change). We observed stronger associations between fast-food outlets and BMI, but not BMI change, among young adults and especially young adults with a medium or high genetic predisposition toward elevated BMI. Our results should be considered as encouragement for policy makers to create healthier environments and a starting point for researchers to identify individuals susceptible to fast-food environments.

AUTHOR CONTRIBUTIONS

Carel-Peter L. van Erpecum: conceptualization; methodology; formal analysis; writing, original draft; writing, review and editing; and visualization. Sander K.R. van Zon: conceptualization; methodology; and writing, review and editing. Tian Xie: conceptualization; methodology; software; and writing, review and editing. Harold Snieder: conceptualization; methodology; and writing, review and editing. Ute Bültmann: conceptualization; methodology; and writing, review and editing. Nynke Smidt: conceptualization; methodology; and writing, review and editing.

ACKNOWLEDGMENTS

The authors acknowledge the services of Lifelines and participants.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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How to cite this article: van Erpecum C-PL, van Zon SKR, Xie T, Snieder H, Bültmann U, Smidt N. Fast-food environments and BMI changes in the Dutch adult general population: the Lifelines cohort. *Obesity (Silver Spring)*. 2023;31(8):2159-2170. doi:10.1002/oby.23781