

Impact of Commuting Mode on Obesity Among a Working Population in Beijing, China: Adjusting for Air Pollution

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Background: Few studies have considered the interplay between commuting mode and air pollution on obesity. The aim of this study was to examine whether workplace air pollutants exposure modifying the associations between different commuting mode and obesity.

Methods: A cross-sectional study of workers in Beijing was conducted in 2016. The study sample comprised 10,524 participants aged 18 to 65 years old. Outcomes were defined as overall obesity (BMI ≥ 28 kg/m²) and abdominal obesity (WC ≥ 85 cm in men and WC ≥ 80 cm in women). Commuting modes were divided into walking, cycling, bus, subway, and car or taxi. Logistic regression models were used to estimate odds ratios relating commuting mode to overall and abdominal obesity and stratified by gender, controlling for covariates.

Results: The association between commuting mode and obesity was more strongly in men than women. In the fully adjusted models, compared with car or taxi commuters, cycling (men: OR=0.37, 95% CI=0.20 to 0.68) or bus (men: OR=0.58, 95% CI=0.36 to 0.94) counterparts had a lower risk of overall obesity. Compared with car or taxi commuters, walking (men: OR=0.57, 95% CI=0.36 to 0.91), bus (men: OR=0.59, 95% CI=0.39 to 0.89), or subway (men: OR=0.59, 95% CI=0.39 to 0.89) counterparts had a lower risk of abdominal obesity. We observed significant interactions between exposure PM₁₀ and cycling on overall obesity in men. After adjusting for air pollutants, the association between commuting mode and obesity was slightly strengthened.

Conclusion: This study findings indicate that active (walking or cycling) or public (bus or subway) commuting modes were protected factors for overall and abdominal obesity among men. Air pollutants do not obscure the benefits of active or public commuting for obesity. These associations support the policy for increasing active or public commuting as a strategy to reduce the prevalence of obesity.

Keywords: obesity, commuting mode, air pollutant, body mass index, waist circumference, office worker

Plain Language Summary

What is Already Known About This Subject?

It is well known that physical activity is beneficial for health. Active commuting (walking, cycling) as a form of physical activity is associated with lower risk of obesity. The scientific evidence on commuting mode or air pollutants in relation to risk of obesity is not entirely consistent. Little is known about the association between commuting mode and obesity, after adjusted for the effects of air pollutants.

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What are the New Findings?

Men office worker had a higher prevalence of obesity than women, especially abdominal obesity. Considering the effects of air pollutants, a steady negative association between active (walking, cycling) or public (bus, subway) commuting mode and obesity, while these associations were only found in men.

How Might This Impact on Policy or Clinical Practice in the Foreseeable Future?

Increasing active (walking, cycling) or public (bus, subway) commuting as a strategy to reduce the prevalence of obesity and improve public health.

Introduction

Obesity has become a pandemic in China,^{1,2} and it is one of the major risk factors for noncommunicable chronic diseases (NCDs), such as cardiovascular disease (CVD),³ metabolic disorders, and premature mortality.^{4–6} Over half of the Chinese population is overweight or obese, and in mega-cities such as Beijing, overweight and obesity have always been serious problems.^{7,8} With the rapid economic development of China, great changes have taken place in the lifestyle and physical activity habits of the inhabitants.⁸ Among these changes, multiple factors such as lack of physical activity, unhealthy lifestyles, working stress, and environmental pollution may contribute to increased obesity and NCDs.^{2,9,10}

Air pollution, especially particulate matter with an aerodynamic diameter smaller than 10 μm (PM_{10}) or 2.5 μm ($\text{PM}_{2.5}$), has been improving in recent years but in winter is worsening in Beijing.¹¹ Beijing is a crowded metropolis where traffic emissions account for a large share of $\text{PM}_{2.5}$ concentration.¹² The working population is a subtype of population. They faced the heavy traffic, life insecurity and heavy work pressure in Beijing, making them more prone to developing obesity. Physical activity is important for office employees, especially for those who are exposed to the harmfulness of sedentary work.¹³ Integrating physical activity into daily life is recognized as a potential way to prevent obesity and chronic diseases.^{14,15} Active commuting, which refers to walking and cycling, is positively correlated with the benefits of physical activity.¹⁶ Nationwide, active commuting is promoted as a way of incorporating physical activity into daily life to reduce the rates of NCDs.¹⁶ There are quite a few confounding factors in the associations between

different commuting modes and obesity, and some uncertainties about the associations still exist. Exposure to traffic microenvironments was reported to be associated with some health risks such as obesity and cardiopulmonary diseases.^{17–20} In addition, air pollution is associated with inflammation around the bronchi, which may increase systemic inflammation and oxidative stress leading to obesity.²¹ Animal experiments showed that air pollution can lead to weight gain and cardiorespiratory and metabolic dysfunction.²²

Previous studies have consistently suggested that walking or cycling commuters have lower BMIs than car commuters^{23–26} and that exposure to air pollutants associated with inflammatory adipokines derangements²⁷ and adverse health outcomes.^{28,29} Some studies have shown that active commuting should not be limited to walking and cycling but should also include public transportation.^{25,30} In Beijing, many people live too far from the workplace to commute by walking or cycling. During rush hour, traffic congestion and bad weather conditions such as haze can occur. However, most studies have not accounted for the impact of air pollutants on the relationship between commuting mode and health outcomes. Thus, the aim of this research was to investigate the association between commuting mode and overall and abdominal obesity in a sample of Chinese working adults after adjustment for air pollutants and other potential confounders.

Materials and Methods

Study Design and Data Collection

The study was conducted to provide cross-sectional estimates of the association between obesity and commuting mode among the employees of various enterprises and institutions, which included state-owned enterprises, private enterprises and public institutions. Participants attended health examinations at the Beijing physical examination center. The participants included 11,474 individuals who were recruited via a convenience sampling method from 69 enterprise and public institutions in 7 districts (Chaoyang, Dongcheng, Fengtai, Haidian, Xicheng, Daxing, and Pinggu) in Beijing in 2016. Additional 950 individuals were excluded due to retirement, missing data or the presence of CVD, cerebrovascular disease, or cancer. Finally, 10,524 subjects were included in this research. [Figure S1](#) illustrated a flowchart of the selection of the study subjects. The

research was approved by the Ethics Committee of Capital Medical University (NO: 2013SY26) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the participating subjects prior to data collection.

The subjects received health examinations at the Beijing physical examination center by experienced doctors. Height and body weight were measured while the participant was barefoot and wearing minimal clothing. Body mass index (BMI) was calculated using the standard equation $\text{weight (kg)}/\text{height (m)}^2$. Waist circumference (WC) was measured at the midway point between the top of the hipbone and the bottom of the ribs.

Demographic data were obtained by a questionnaire. The questionnaire was investigated by two trained investigators. Participants were asked, "What is the main type of transport that you often use to get to and from work?" Participants were allowed to select one of the following options: walking, cycling, bus, subway, and car or taxi. There was also some information on lifestyle factors: education level, self-reported work pressure, intensity of physical activity, frequency of physical activity, sleep duration, smoking status, alcohol consumption status, dietary habits, grain consumption, medical history of hypertension, and medical history of diabetes. Current or previous smoking was defined as an adult who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes or had quit smoking at the time of interview. Current or previous drinking was defined as at least 12 drinks in any one year in lifetime or had quit drinking at the time of interview. Excessive meat intake was defined as at least once a week daily intake of 75 g or more of meat. Excessive edible oil intake was defined as at least once a week daily intake of 30 g or more of edible oil. Excessive salt intake was defined as at least once a week daily intake of 6 g or more of salt. Excessive sweet food intake was defined as at least once a week daily intake of 25 g or more of sugar.

Concentrations of air pollutants, including carbon monoxide (CO), nitrogen dioxide (NO₂), ozone (O₃), PM₁₀, PM_{2.5} and sulfur dioxide (SO₂), were measured at the fixed-site monitoring stations closest to the participants' workplaces. All air pollutant data were obtained from a website platform (<http://zx.bjmemc.com.cn/>) by the Beijing Environmental Protection Bureau (BEPB). Excluded the outliers in the hourly measured values of each monitoring station, the

average annual concentration of each air pollutant was calculated by the average daily concentration of each air pollutant. Considering that obesity is a chronic disease and the long-term effect of air pollutants on health, the annual average concentrations of air pollutants collected during the year prior to the participant's physical examination were used.

Outcomes

Obesity is defined as abnormal or excessive fat accumulation that may impair health. For adults, the Chinese standard of overall obesity was defined as a BMI greater than or equal to 28 kg/m². Abdominal obesity was defined as WC ≥ 85 cm in men and ≥ 80 cm in women.³¹

Statistical Analysis

The characteristics of the participants are presented as the mean with the standard deviation (SD) or the median with the interquartile range (IQR) for quantitative variables or with a percentage for categorical variables. The associations between the commuting mode and overall and abdominal obesity were explored using logistic regression analyses (overall obesity, no/yes; abdominal obesity, no/yes), resulting in an odds ratio (OR) with a 95% confidence interval (95% CI). Considering the high correlation among air pollutants (Table S1), we only keep PM₁₀ in model 3. The results of other pollutants were shown in Table S3 and S4. Model 1 was unadjusted. In model 2, we adjusted for age, gender, education, commuting time per day, self-reported work stress, physical activity frequency and intensity, sleep duration, smoking status, alcohol consumption status, proportion of meat and vegetable intake, dietary preferences and medical history of hypertension and diabetes. Model 3 was additionally adjusted for PM₁₀ exposure. We added an interact term on model 3 to test the interaction between air pollutant and commuting mode.

To examine whether any associations were modified by leisure-time physical activity frequency or intensity, we performed sensitivity analyses stratified by leisure-time physical activity frequency or intensity.

All statistical analyses were carried out with the SAS software package (version 9.4; SAS Institute, Inc.). Statistical significance was indicated by a two-tailed *P* value less than 0.05.

Results

Figure 1 shows the distribution of monitoring stations and workplaces in Beijing. The main characteristics of the study participants according to gender are summarized in

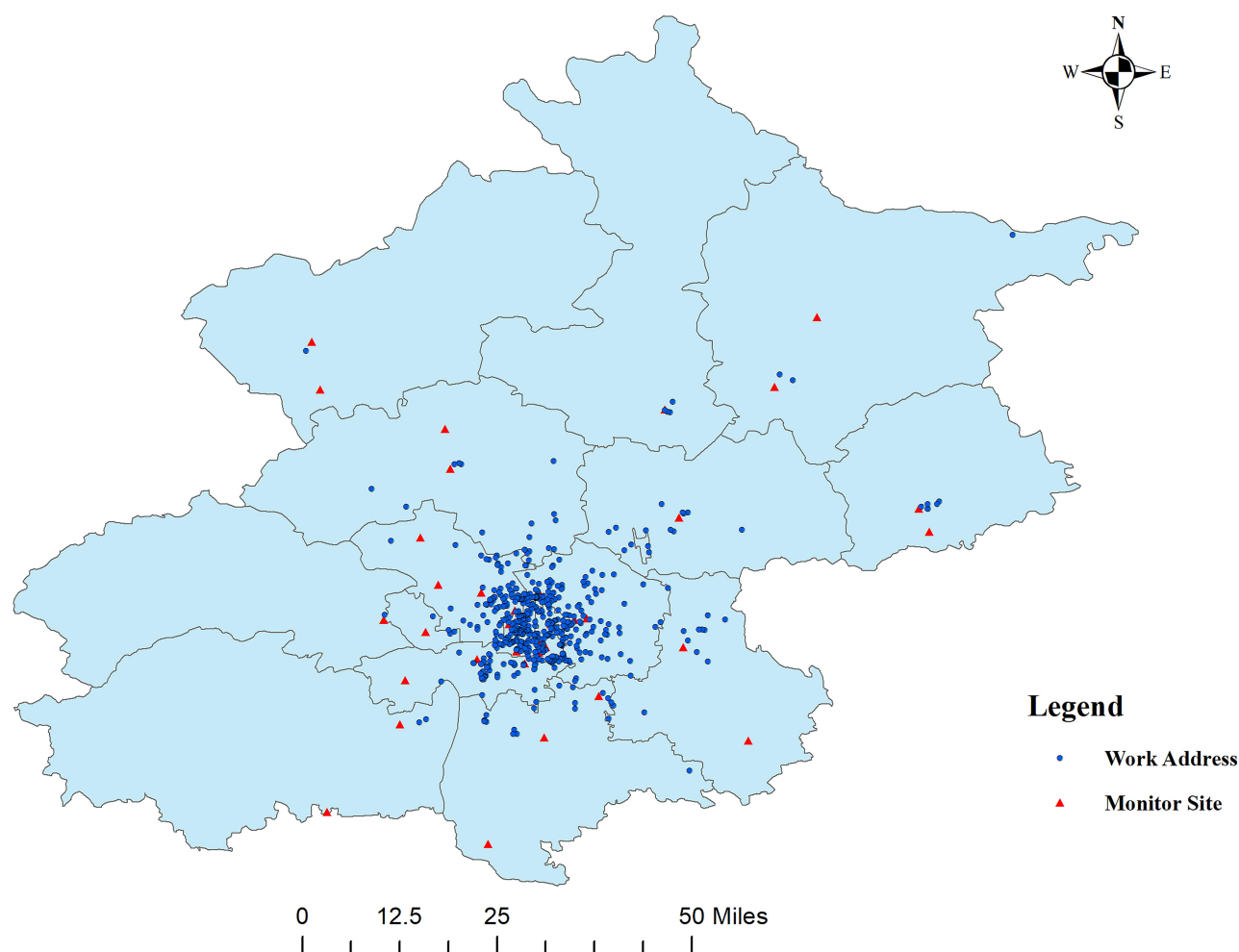


Figure 1 Distributions of air pollutants monitoring stations and workplaces in Beijing.

Table 1. Of the 10,524 employees of enterprises and public institutions included in this study, the most common commuting mode was car or taxi in men (28.77%) and subway in women (27.95%). A total of 24.97% of men chose active commuting (walking or cycling) compared with 23.31% of women. Self-reported high level of work stress was higher in men than women (42.76% of men and 34.30% of women, $P < 0.0001$). The frequency of physical activity was slightly higher in men than women, 15.46% of men were more than once every day and 11.20% of women ($P < 0.0001$), as well as the intensity of physical activity, 8.91% of men were vigorous level and 3.31% of women ($P < 0.0001$). In addition, men were greater likelihood of smoking (41.23% of men and 2.29% of women, $P < 0.0001$) and drinking (61.96% of men and 12.98% of women, $P < 0.0001$) than women. In terms of diet, the proportion of excessive meat (16.98% of men and 7.87% of women, $P < 0.0001$), edible oil (6.79% of men and

4.06% of women, $P < 0.0001$) and salt intake (16.98% of men and 7.87% of women, $P < 0.0001$) in men were significantly greater than women, while the proportion of vegetarian (10.57% of men and 16.31% of women, $P < 0.0001$) and excessive sweet food intake (7.94% of men and 10.71% of women, $P < 0.0001$) in women were significantly greater than men. The sleep duration was similar between men and women.

Figure 2 shows the prevalence rates of overall and abdominal obesity. In this study, 1418 (13.47%) had overall obesity and 4712 (44.77%) had abdominal obesity. Compared with commuters utilizing other modes, car or taxi commuters, followed by cyclists, had a higher prevalence of obesity, regardless of whether overall and abdominal obesity was being analyzed. Men employees were more likely to have obesity than women ($P < 0.0001$).

The summary statistics of air pollutants categories by commuting mode during the study period in Beijing are

Table 1 The Main Characteristics of Participates for Men and Women

Variables	Total(n=10,524)	Men(n=5847)	Women(n=4677)	P value ^a
Overall obesity	1418(13.47)	1135(19.41)	283(6.05)	<0.0001
Abdominal obesity	4712(44.77)	3758(64.27)	954(20.4)	<0.0001
Main commuting mode				<0.0001
Car or Taxi	2830(26.89)	1682(28.77)	1148(24.55)	
Walking	1356(12.88)	713(12.19)	643(13.75)	
Cycling	1194(11.35)	747(12.78)	447(9.56)	
Bus	2540(24.14)	1408(24.08)	1132(24.20)	
Subway	2604(24.74)	1297(22.18)	1307(27.95)	
Commuting time (hour), median (IQR)	1.9(1.60–2.00)	2.00(1.90–2.00)	1.90(1.00–2.00)	<0.0001 ^b
Age (years)				<0.0001
18–44	7188(68.30)	3747(64.08)	3441(73.57)	
45–65	3336(31.70)	2100(35.92)	1236(26.43)	
Education level				<0.0001
High school or lower	1336(12.69)	949(16.23)	387(8.27)	
College	6963(66.16)	3913(66.92)	3050(65.21)	
Graduate or above	2225(21.14)	985(16.85)	1240(26.51)	
Self-reported work stress				<0.0001
Low	1581(15.02)	815(13.94)	766(16.38)	
Moderate	4839(45.98)	2532(43.30)	2307(49.33)	
High	4104(39.00)	2500(42.76)	1604(34.30)	
Physical activity frequency				<0.0001
Less than once every week	3920(37.25)	2103(35.97)	1817(38.85)	
More than once every week	5176(49.18)	2840(48.57)	2336(49.95)	
More than once every day	1428(13.57)	904(15.46)	524(11.20)	
Physical activity intensity				<0.0001
Mild	5307(50.43)	2676(45.77)	2631(56.25)	
Moderate	4541(43.15)	2650(45.32)	1891(40.43)	
Vigorous	676(6.42)	521(8.91)	155(3.31)	
Sleep duration				0.2855
< 6 hours/day	7184(68.26)	3966(67.83)	3218(68.80)	
≥ 6 hours/day	3340(31.74)	1881(32.17)	1459(31.20)	
Current or previous smoking	2518(23.93)	2411(41.23)	107(2.29)	<0.0001
Current or previous drinking	4230(40.19)	3623(61.96)	607(12.98)	<0.0001
Vegetarian	1381(13.12)	618(10.57)	763(16.31)	<0.0001
Excessive meat intake	1361(12.93)	993(16.98)	368(7.87)	<0.0001
Excessive edible oil intake	587(5.58)	397(6.79)	190(4.06)	<0.0001
Excessive salt intake	2199(20.9)	1449(24.78)	750(16.04)	<0.0001
Excessive sweet food intake	965(9.17)	464(7.94)	501(10.71)	<0.0001
Medication history for hypertension	921(8.75)	676(11.56)	245(5.24)	<0.0001
Medication history for diabetes	195(1.85)	161(2.75)	34(0.73)	<0.0001

Notes: Values reported as numbers (percentages), unless otherwise noted. Current or previous smoking: An adult who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes or had quit smoking at the time of interview. Current or previous drinking: At least 12 drinks in any one year in lifetime or had quit drinking at the time of interview. Excessive meat intake: at least once a week daily intake 75 g or more of meat. Excessive edible oil intake: at least once a week daily intake 30 g or more of edible oil. Excessive salt intake: at least once a week daily intake 6 g or more of salt. Excessive sweet food intake: at least once a week daily intake 25 g or more of sugar. ^aThe results of χ^2 test, where the null hypothesis was that the difference between men and women group was equal to 0. ^bThe results of non-parametric test, where the null hypothesis was that the difference between men and women group was equal to 0.

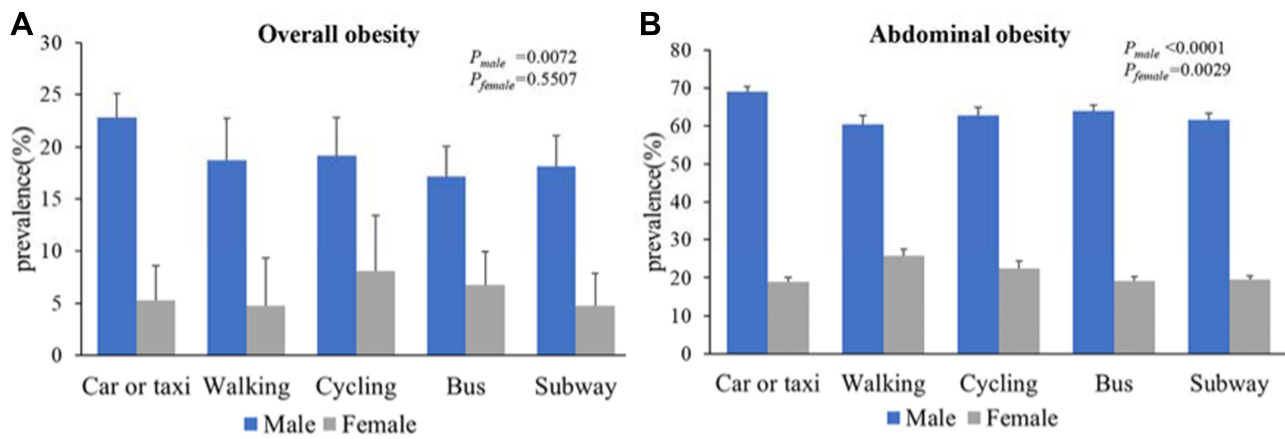


Figure 2 Prevalence of overall and abdominal obesity among the study participants. **(A)** Prevalence of overall obesity by commuting mode stratified by gender. **(B)** Prevalence of abdominal obesity by commuting mode stratified by gender. **Abbreviations:** P_{male} , the P-value for differences in prevalence of overall or abdominal obesity with different commuting mode among men; P_{female} , the P-value for differences in prevalence of overall or abdominal obesity with different commuting mode among women.

shown in [Table S2](#). The means (SDs) of the air pollutants were 1.19 (0.22) mg/m³ for CO, 48.18 (14.76) µg/m³ for NO₂, 40.66 (10.24) µg/m³ for O₃; 97.60 (15.52) µg/m³ for PM₁₀, 73.97 (11.42) µg/m³ for PM_{2.5} and 11.18 (2.82) µg/m³ for SO₂.

[Figure 3](#) shows the associations of the commuting modes with overall obesity after adjusting for potential confounders. In the overall obesity analysis in men, without adjusting for any confounders, compared with car or taxi commuters, walking, cycling, bus and subway commuters had an adjusted odds ratio of 0.70 (95% CI=0.56 to 0.88), 0.80 (95% CI=0.64 to 0.99), 0.82 (95% CI=0.68 to

0.97) and 0.77 (95% CI=0.64 to 0.92), respectively. In men, after adjusting for demographic, health and behavioral factors, walking (OR=0.72, 95% CI=0.57 to 0.91), cycling (OR=0.80, 95% CI=0.64 to 1.00), bus (OR=0.81, 95% CI=0.67 to 0.97) and subway (OR=0.78, 95% CI=0.65 to 0.95) commuters had a lower risk of overall obesity. After adjusting for PM₁₀, cycling (OR=0.37, 95% CI=0.20 to 0.68, $P_{interaction}=0.007$) and bus (OR=0.58, 95% CI=0.36 to 0.94, $P_{interaction}=0.132$) commuters still had a lower risk of overall obesity in the analysis of the men. While in the female group, no significant association was observed between commuting mode and overall

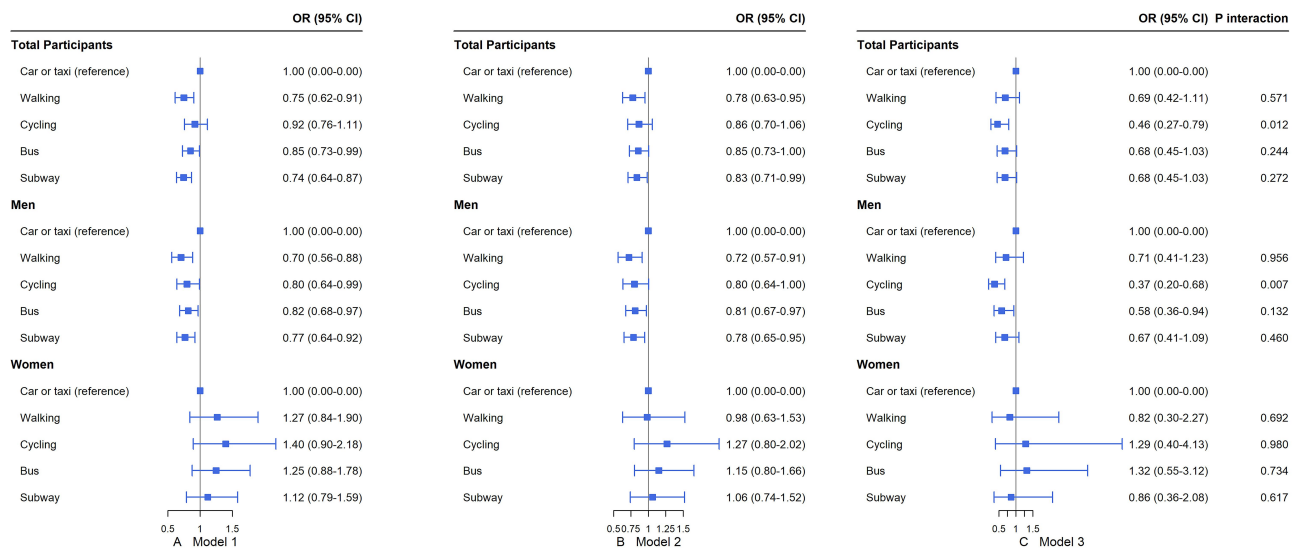


Figure 3 Association of commuting mode with overall obesity, stratified by gender (n=10,524). Model 1: unadjusted. Model 2: adjusted for age, gender, education, commuting time per day, self-reported work stress, physical activity frequency and intensity, sleep duration, smoking status, alcohol consumption status, proportion of meat and vegetable intake, dietary preferences and medical history of hypertension and diabetes. Model 3: adjusted for the factors in Model 2 + PM₁₀.

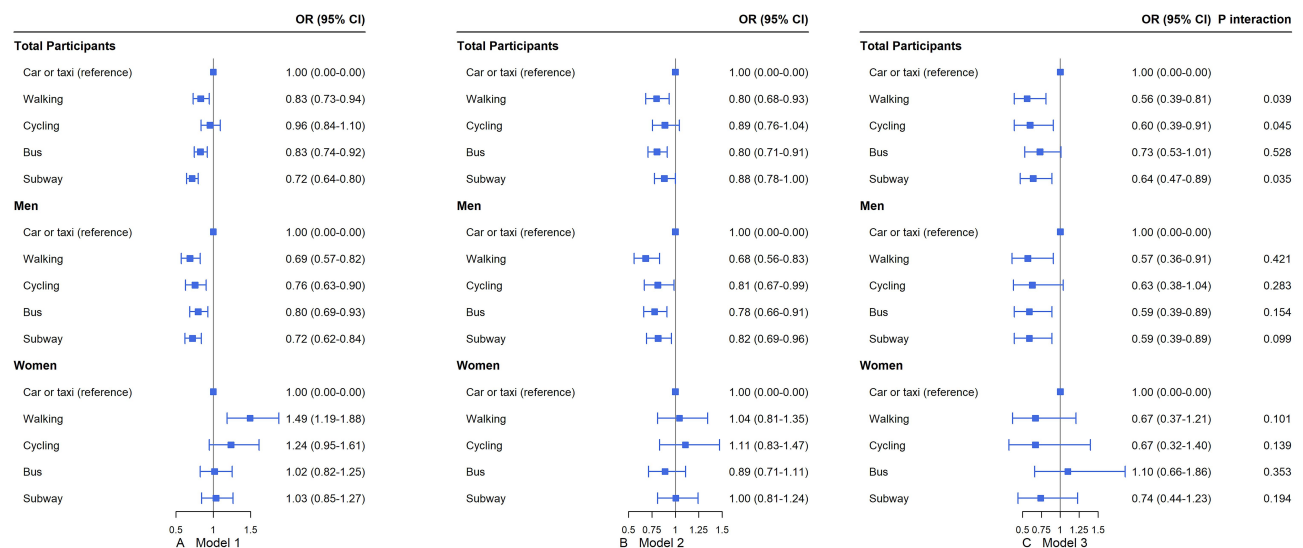


Figure 4 Association of commuting mode with abdominal obesity stratified by gender (n=10,524). Model 1: unadjusted. Model 2: adjusted for age, gender, education, commuting time per day, self-reported work stress, physical activity frequency and intensity, sleep duration, smoking status, alcohol consumption status, proportion of meat and vegetable intake, dietary preferences and medical history of hypertension and diabetes. Model 3: adjusted for the factors in Model 2 + PM₁₀.

obesity in the fully adjusted model. Figure 4 shows the associations of commuting mode with abdominal obesity after adjusting for potential confounders. Similarly, in fully adjusted model, walking (OR=0.57, 95% CI=0.36 to 0.91, $P_{interaction}=0.421$), bus (OR=0.59, 95% CI=0.39 to 0.89, $P_{interaction}=0.154$) and subway (OR=0.59, 95% CI=0.39 to 0.89, $P_{interaction}=0.099$) commuters still had a lower risk of abdominal obesity in the analysis of the men. No significant associations were observed between commuting mode and abdominal obesity in women. Across all models, compared with car or taxi commuters, bus commuters were always associated with a lower risk of overall and abdominal obesity in men. We observed significant interactions between exposure to PM₁₀ ($P_{interaction}=0.007$) and cycling, SO₂ ($P_{interaction}=0.0399$) and walking on overall obesity in men. Exposure to SO₂ ($P_{interaction}=0.0408$) and bus, SO₂ ($P_{interaction}=0.0418$) and subway had an interact effect on overall obesity in women. Exposure to O₃ ($P_{interaction}=0.0331$) and walking had an interact effect on abdominal obesity in men. The results of other pollutants were different from PM₁₀ (Table S3 and S4). After adjusting for PM_{2.5}, cycling (OR=0.50, 95% CI=0.26 to 0.97, $P_{interaction}=0.1351$) commuters had a lower risk of overall obesity in the analysis of the men. After adjusting for SO₂, subway (OR=0.52, 95% CI=0.30 to 0.91, $P_{interaction}=0.1151$) commuters had a lower risk of overall obesity in the analysis of the men, while bus (OR=3.48, 95% CI=1.12 to 10.85, $P_{interaction}=0.0408$) and subway (OR=3.17, 95% CI=1.03 to 9.75, $P_{interaction}$

=0.0418) commuters had a higher risk of overall obesity in women. After adjusting for O₃, walking (OR=0.45, 95% CI=0.25 to 0.80, $P_{interaction}=0.0738$) and bus (OR=0.58, 95% CI=0.36 to 0.93, $P_{interaction}=0.1386$) commuters had a lower risk of overall obesity and walking (OR=0.43, 95% CI=0.27 to 0.68, $P_{interaction}=0.0331$) commuters had a lower risk of abdominal obesity in the analysis of the men.

The results from the sensitivity analyses of subsamples of leisure-time physical activity frequency or intensity were similar (Table S5–S8). In the physical activity frequency or intensity subsamples, walking, cycling and bus were always associated with a lower risk of obesity in the lower level of physical activity frequency or intensity.

Discussion

Commuting by walking, cycling, bus or subway was associated with a lower risk of obesity, no matter overall or abdominal obesity. However, bus was associated with the lowest risk of obesity, regardless of whether overall or abdominal obesity was being analyzed in male employees. These results revealed that active commuting and public commuting can be seen as a form of daily physical activity.³² Moreover, compared with commuting by car or taxi, those who travelled by active commuting (walking) or public commuting (bus or subway) had a lower risk of abdominal obesity, and this association was especially strong for men. Comprehensively adjusting for confounders and additionally adjusting for the impacts of the air

pollutants did not attenuate the observed associations. The largest and most significant associations were observed for bus commuters versus car or taxi commuters. These results validate findings from other studies that show that active commuting or public commuting are associated with a lower risk of obesity.^{30,33–35}

The prevalence of abdominal obesity in the working population was approximately three times that of overall obesity. To some extent, this finding reflects the trend of obesity in China in recent years.^{36,37} We found that the association between active commuting and obesity was only present in men. In this study, women have lower prevalence of obesity, we did not find a significant association between commuting mode and obesity in women. Previous studies showed that stress is positively correlated with obesity.³⁸ In this study, men reported higher self-reported work stress than women, which partly explains the higher prevalence of obesity in men than women. The gender difference in the association between commuting mode and obesity found in this study warrants further research.

Existing studies assessing the relationship between commuting mode and obesity have yielded varied results. Flint et al²⁶ reported an association between active commuting and obesity. Commuting modes and leisure-time physical activities were associated with cardiovascular risk factors in previous studies^{23,39,40} However, few studies have previously reported the relationship between commuting mode and obesity after adjusting for air pollutants. The results of our study showed that the probability of experiencing obesity in people who commuted by walking, cycling, bus or subway was lower than that of those who commuted by car or taxi to work. Our findings are consistent with those of previous studies.^{24,34}

This study explored the relationships between commuting mode and overall and abdominal obesity using a large, representative dataset from the working population in Beijing, China. The results of this study showed a robust, significant association between commuting mode and both overall and abdominal obesity. Our results suggested that different air pollutants had different effects on commuting mode and obesity. The interaction between air pollutants and commuting modes varies among air pollutants. The results of this study can only indicate that air pollutants may have an impact on obesity, which needs further study in the future.

Strengths and Limitations

To observe more robust results, we used two distinct obesity definitions to investigate the association between commuting mode and obesity outcomes. In this way, we reduced the limitation of using BMI to define obesity and addressed the concerns of the effect of WC. An increasing number of office workers suffer from abdominal obesity, rather than overall obesity, due to sedentary behavior and lack of physical activity.

This study has several limitations. As one of the most important confounding factors, we did not have information on dietary energy intake. To reduce bias, we adjusted some diet-related factors such as excessive meat intake, excessive edible oil intake, excessive salt intake and excessive sweet food intake in daily diet. In addition, sedentary behavior is a potential confounder for obesity. However, we did not have data on sedentary behavior. The third limitation is that the information about home address was lacking in our research, and the concentration of air pollutants in the subjects in this study was based on monitoring stations near the workplace rather than on more precise personal exposure to air pollutants. Further studies should measure individual exposure to air pollutants for more accurate results.

Perspective

The results showed that, compared with car or taxi commuting, active or public commuting was associated with a significantly lower risk of obesity. The findings in our study support the idea that efforts to increase bus commuting should be addressed as a strategy to prevent and reduce the prevalence of obesity, especially among male workers.

Ethics Statement

The research was approved by the Ethics Committee of Capital Medical University (NO: 2013SY26) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the participating subjects prior to data collection.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors report no conflicts of interest for this work.

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