The Effects of Smoking on Metabolic Syndrome and Its Components Using Causal Methods in the Iranian Population

Abstract

Background: The aim of this study was to estimate the effect of smoking on metabolic syndrome (MS) and its components applying inverse probability-of-treatment weighting (IPTW) and propensity score (PS) matching. **Methods:** Using data from Tehran Lipid and Glucose Study, 4857 participants aged over 20 years with information on smoking and confounders in the third phase (2005–2008) were included, and the MS was assessed in the fifth phase (2011–2014). IPTW and PS matching were used to adjust for confounders. **Results:** Based on average treatment effect (ATE) estimates, smoking decreased the risk of hypertension (RR: 0.62; 95% CI: 0.43, 0.88), but increased the risk of low HDL cholesterol (1.20; 0.98, 1.48). Similarly, the average treatment effect in the treated (ATT) estimates using IPTW and PS matching suggested that smoking decreased the risk of hypertension (0.63; 0.52, 0.76, and 0.68; 0.54, 0.85), and increased the risk of low HDL cholesterol (1.24; 1.07, 1.43, and 1.28; 1.06, 1.54), respectively. **Conclusions:** Smoking seems to increase the risk of low HDL cholesterol but decreases the risk of hypertension.

Keywords: *Metabolic syndrome, propensity score, smoking.*

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Introduction

Metabolic syndrome (MS) is a set of conditions including central obesity, high blood pressure (BP), increased fasting blood sugar (FBS), increased triglycerides, and decreased high-density lipoprotein cholesterol (HDL-C).[1] The prevalence of MS is globally increasing and, depending on some background factors, ranges from less than 10% to 84%.[2] MS patients are at risk of a two-fold increase in type 2 diabetes and a five-fold increase in cardiovascular disease over the next 5 and 10 years, respectively.[2]

Modifications of life styles such as smoking are useful for chronic diseases prevention.[3] Smoking is associated with many noncommunicable diseases and contributes to mortality and disability-adjusted life year (DALYs).[4,5] According to the world health organization, there will be 1.5 billion smokers worldwide by 2050.[5] The relationship between smoking and MS,[6,7] BP,[8,9] abdominal obesity,[10] FBS,[11] and triglycerides[9,12] has been already studied using conventional regression for confounding adjustment. An alternative is propensity score (PS)

methods. PS, defined as the probability of exposure given the set of confounders,[13] can be used in different procedures for confounding adjustment: matching, inverse probability-of-treatment weighting (IPTW), stratification, and regression adjustment.[14-17]

PS methods are preferred to outcome regression for inferring causality because i) it is easier to determine whether the exposure models are correctly specified in terms of yielding covariate-balancing PSs using standardized differences, ii) these methods effectively emulate a randomized experiment without any reference to the outcome, and iii) the overlap in the distribution of confounders can be explicitly assessed between two exposure groups: the small number of matched subjects or huge inverse probability-of-treatment weights indicate low overlap.[18] The aim of this study is to estimate the effect of smoking on MS and its components using IPTW and PS matching.

Methods

Using the third phase data (2005-2008) of Tehran Lipid and Glucose cohort Study (TLGS) as the baseline, 4857 participants aged over 20 years without MS and with information on smoking

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and confounders were selected. MS was assessed in the fifth phase (2011–2014). This study was approved by the Research Council of Research Institute for Endocrine Sciences of Shahid Beheshti University of Medical Sciences, and a consent form was obtained from all participants.

The exposure was cigarette smoking status assessed by the question: "is person smoking daily?". The outcome was MS, defined as having at least three out of the following variables: abdominal obesity (waist circumference ≥95 cm), low HDL-C (<40 in men or <50 mg/dL in women), hypertriglyceridemia (TG ≥150 mg/dL), hypertension (systolic BP ≥130 or diastolic BP ≥85 mmHg) and impaired blood glucose (FBS ≥100 mg/dL).[19-21]

The confounders were identified using a causal diagram [Figure 1] for the study population.[22-27] The minimally sufficient set for confounding adjustment, derived based on Pearl's back-door criterion,[28] included gender, age, physical activity, marital status, education, and job, measured by a questionnaire, as well as the unmeasured variables income and alcohol. Fractional polynomials were used to identify any nonlinear association between age and smoking in the PS model.[29]

Statistical methods

IPTW was used to adjust for confounders. We first estimated PS through logistic regression, with smoking as the response variable and confounders as predictors. Then the average treatment effect (ATE) was estimated using weighted risk ratio (RR) between smoking and MS with weights equal to 1/PS for the smokers and 1/(1−PS) for the non-smokers. Moreover, the average treatment effect in the treated (ATT) was estimated with weights equal to 1 for the smokers and PS/(1−PS) for the non-smokers.[30,31] IPTW produces a pseudo-population in which confounders do not predict the exposure, and the effect in the pseudo-population is the same as that in the population.

Confounders were also adjusted for using PS matching. A PS-matched dataset was created by matching, without replacement, one unexposed person to one exposed based
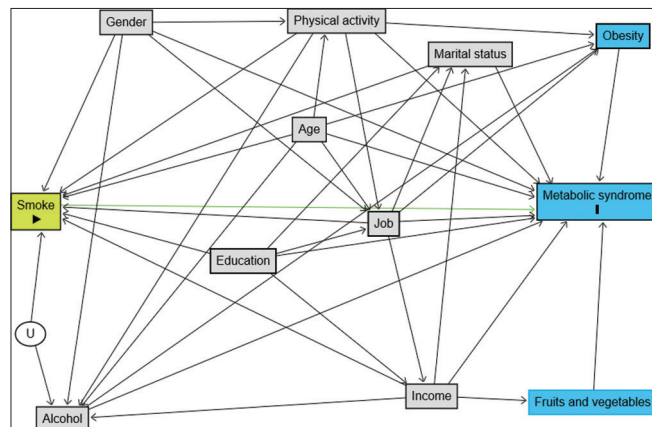
on the nearest value of PS (±0.05).[32] Then the ATT effect was estimated using the RR between smoking and MS in the matched sample.[18]

The 95% confidence intervals (CIs) for the IPTW estimates were derived using robust standard errors.[33] The 95% CIs for the PS matching was obtained based on nonparametric bootstrapping by 1000 repetitions with 2.5th and 97.5th percentiles as 95% confidence limits.[34]

The correct specification of the PS model was assessed based on the balance of measured confounders between exposure groups in the matched sample for PS matching, and in the weighted sample for the IPTW. The standardized difference was used to compare the mean and proportion of continuous and binary confounders between the exposed and unexposed, respectively. The standardized difference for continuous confounders is

$$d = \frac{(\overline{x}_{exposed} - \overline{x}_{unexposed})}{\sqrt{\dfrac{s^2_{exposed} + s^2_{unexposed}}{2}}}$$

Where $\overline{x}_{exposed}$ and $\overline{x}_{unexposed}$ are the mean estimates, and $s^2_{exposed}$ and $s^2_{unexposed}$ are variance estimates in exposed and unexposed, respectively.

The standardized difference for binary confounders is

$$d = \frac{\hat{p}_{exposed} - \hat{p}_{unexposed}}{\sqrt{\dfrac{\hat{p}_{exposed}\left(1 - \hat{p}_{exposed}\right) + \hat{p}_{unexposed}(1 - \hat{p}_{unexposed})}{2}}}$$

Figure 1: Causal diagram for the effect of smoking on MS

Table 1: Baseline characteristics of the study participants

Characteristic	Smokers, *n* (%)	Non-smokers, *n* (%)
Gender (female)	74 (14.5)	2885 (66.4)
Age, years, mean (SD)	40.89 (12.67)	38.89 (13.56)
Marital status		
single	102 (19.9)	918 (21.1)
married	391 (76.4)	3233 (74.4)
divorced	13 (2.5)	56 (1.3)
widowed	6 (1.2)	138 (3.2)
Educational certificate		
elementary	57 (11.1)	592 (13.6)
secondary school	98 (19.1)	641 (14.8)
high school	264 (51.6)	2067 (47.6)
associate degree	31 (6.1)	284 (6.5)
BSc	56 (10.9)	653 (15.0)
MSc or higher degrees	6 (1.2)	108 (2.5)
Occupational status		
employed	378 (73.8)	1606 (37.0)
student	11 (2.1)	291 (6.7)
housewife	51 (10.0)	2039 (46.9)
no work with income	46 (9.0)	325 (7.5)
others	26 (5.1)	84 (1.9)
Physical activity (yes)	310 (60.5)	2812 (64.7)

Where $\hat{p}_{exposed}$ and $\hat{p}_{unexposed}$ are the proportion estimates of the binary confounders in the exposed and unexposed, respectively.

A standardized difference of more than 0.1 was considered as an important difference in mean or proportion of confounders between exposure groups.[18] All statistical analyses were performed using stata.

Results

Of 4857 participants, 2959 (60.9%) were female, and the mean (SD) of age was 39.10 (13.48) years. There were 512 (10.5%) cigarette smokers at baseline, and 922 (19.0%) developed MS during the study follow-up. We excluded 25 (0.5%) participants due to missing MS data in phase 5. In PS matching, 511 unexposed were matched to 511 exposed. The mean (SD) of weights for ATE and ATT estimates were 2.02 (5.22) and 0.21 (0.30), respectively. The baseline characteristics of participants have been shown in Table 1. Table 2 represents the standardized differences for confounders in original, weighted and matched data. In the original data, eight variables had standardized differences above 0.1, but in both weighted and matched data all variables had standardized differences less than 0.1, a sufficient balance on the confounders. The effects of smoking on MS and its components have been presented in Table 3. Based on ATE estimates, smoking decreased the risk of hypertension, RR: 0.62 (95% CI: 0.43, 0.88), but increased the risk of low HDL-C: 1.20 (95% CI: 0.98, 1.48). Similarly the ATT estimates using IPTW and PS matching suggested that smoking decreased the risk of hypertension, 0.63 (95% CI: 0.52, 0.76) and 0.68 (95% CI: 0.54, 0.85), and increased the risk of low HDL-C, 1.24 (95% CI: 1.07, 1.43) and 1.28 (95% CI: 1.06, 1.54), respectively. There was no strong evidence against no effect of smoking on MS, abdominal obesity, hypertriglyceridemia and impaired blood glucose.

Discussion

We did not find strong evidence against no effect of smoking on MS using causal methods which are consistent with previous studies.[35,36] However, some studies indicated a positive relationship between smoking and MS.[37,38] The difference in study population, MS definition, and statistical analysis may justify the controversial results.

Our estimates suggest that smoking increases the risk of low HDL-C which is consistent with the results of previous studies.[39,40] This finding can be explained by the fact that smoking decreases lipid metabolism through diminished lipoprotein lipase activity.[40] Also, nicotine can cause lipolysis which in turn may reduce HDL-C.[6]

Our analyses revealed that smoking lowers BP. According to some studies, smokers have a lower risk of hypertension and a cluster analysis on a national survey in Iran showed that people in a cluster of smokers were less likely to experience elevated BP, though they had a very high level of work-related physical activity.[41-43] These results may be interpreted as an indirect protective effect of smoking on BP through the body weight.[44] However,

Table 2: Standardized differences for confounders

Confounder	Original data	Weighted data	Matched data
Gender (male)	1.248	0.023	0.006
Age) year)	0.184	0.018	0.004
Marital status			
Single	0.030	0.015	0.005
divorced	0.091	0.017	0.000
widowed	0.138	0.036	0.019
Educational certificate			
elementary	0.076	0.086	0.019
secondary school	0.117	0.014	0.000
associate degree	0.020	0.007	0.008
BSc	0.122	0.006	0.000
MSc or higher degrees	0.098	0.064	0.017
Occupational status			
student	0.223	0.002	0.000
housewife	0.898	0.023	0.006
no work with income	0.055	0.045	0.007
others	0.172	0.010	0.048
Physical activity	0.086	0.020	0.008

Table 3: The ATE and ATT estimates of the effect of smoking on MS and its components using IPTW and PS matching

	Risk Ratio (95% CI) (*P*)			
	Unweighted	ATE using IPTW (*n*: 4857)	ATT using IPTW (*n*: 4857)	ATT using PS matching (*n*: 1022)
MS	1.00 (0.83, 1.21) (0.92)	0.78 (0.55, 1.09) (0.15)	0.83 (0.68, 0.1.02) (0.08)	0.84 (0.66, 1.07) (0.16)
abdominal obesity	1.10 (0.98, 1.24) (0.07)	0.86 (0.69, 1.08) (0.20)	0.89 (0.78, 1.00) (0.06)	0.86 (0.75, 1.00) (0.06)
hypertriglyceridemia	1.30 (1.15, 1.48) (<0.001)	1.10 (0.87, 1.38) (0.39)	1.08 (0.95, 1.24) (0.20)	1.14 (0.96, 1.36) (0.11)
HDL-C	1.01 (0.89, 0.1.15) (0.77)	1.20 (0.98, 1.48) (0.06)	1.24 (1.07, 1.43) (0.003)	1.28 (1.06, 1.54) (0.009)
hypertension	0.84 (0.69, 1.09) (0.07)	0.62 (0.43, 0.88) (0.009)	0.63 (0.52, 0.76) (<0.001)	0.68 (0.54, 0.85) (0.001)
impaired blood glucose	1.24 (1.06, 1.44) (0.005)	0.99 (0.74, 1.32) (0.96)	1.04 (0.88, 1.22) (0.61)	0.97 (0.80, 1.19) (0.83)

Abbreviations: MS: metabolic syndrome, HDL-C: HDL cholostrol, ATE: average treatment effect, IPTW: inverse probability-of-treatment weighting, ATT: average treatment effect in the treated, PS: propensity score, CI: confidence interval. Notes: Estimates were adjusted for gender, age, physical activity, marital status, education, and job.

some studies indicated a higher risk of hypertension for the smokers.[45,46] Moreover, previous studies have shown the positive effect of smoking on cardiovascular disease (2-6 times for >20 vs. <10 cigarette per day)[47,48] which should always be considered as an important factor.

Our study had some limitations. The confounders alcohol consumption and income, were not available. Also there was measurement bias as smoking was dichotomized and self-reported. Finally some confounders like physical activity had measurement error leading to residual confounding.

Conclusions

In summary, there was no strong evidence against no effect of smoking on MS, abdominal obesity, hypertriglyceridemia and impaired blood glucose. Smoking seems to increase the risk of low HDL-Cbut decrease the risk of hypertension. More studies are needed to understand better if and how smoking affects MS and its components.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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