Estimating the Marginal Causal Effect and Potential Impact of Waterpipe Smoking on Multiple Sclerosis Using Targeted Maximum Likelihood Estimation Method: a Large Population-Based Incident Case-Control Study

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Data is available whenever needed.

ABSTRACT

There are few if any reports regarding the role of lifetime waterpipe smoking in multiple sclerosis (MS) etiology. The authors investigated the association between waterpipe and MS, adjusted for confounders. This was a population-based incident case-control study conducted in Tehran, Iran. Cases (n=547) were 15–50-year-old patients identified from the Iranian Multiple Sclerosis Society between 2013 and 2015. Population-based controls (n=1057) were 15–50-year old recruited by random digit telephone dialing. A double robust estimator method known as targeted maximum likelihood estimator (TMLE) was used to estimate the marginal risk ratio and odds ratio between waterpipe and MS. The both estimated RR and OR was 1.70 (95% CI: 1.34, 2.17). The population attributable fraction was 21.4% (95% CI: 4.0%, 38.8%). Subject to the limitations of case-control studies in interpreting associations causally, this study suggests that waterpipe use, or its strongly related but undetermined factors, increases the risk of MS. Further epidemiological studies including nested case-control studies are needed to confirm these results.

Keywords: case-control study, causal analysis, multiple sclerosis, targeted maximum likelihood estimator

Abbreviation: ABS: address-based sampling, CI: confidence interval, GLM: Generalized Linear Model, IMSS: Iranian Multiple Sclerosis Society, IPTW: inverse-probability-of-treatment weighting, MRI: magnetic resonance imaging, MBS: model-based standardization, MS: multiple sclerosis, OR: odds ratio, PS: propensity score, RDD: random digit dialing, RR: risk ratio, SF: sampling fractions, SES: socioeconomic status, TMLE: targeted maximum likelihood estimation,

Multiple sclerosis (MS) as a neurodegenerative immune-mediated disease has been known as a leading cause of non-traumatic disability in young adults. Based on 1990–2016 global burden of multiple sclerosis, 18,932 deaths as well as 1,151,478 DALYs (95% CI: 968,605 to 1,345,776) due to multiple sclerosis in 2016 have been reported (1). An observed critical increase in the incidence of MS (from 0.68/100,000 in 1989 to 2.93/100,000 in 2008) has introduced Tehran as a high-risk area (2). Several studies have reported an increasing trend in waterpipe smoking as an emerging global spread health risk behavior particularly among the young (3-6). Similarly, the prevalence of waterpipe smoking has increased alarmingly especially among women in Iran (7, 8). Despite a general public belief of less harmfulness of waterpipe smoking (9, 10), a 10-times higher smoke volume inhaled per smoking session (11, 12) can result in a significant higher exposure to neuro-toxicant chemicals by waterpipe smoking compared to tobacco smoking.

Although the etiology of MS remains poorly understood, there is some evidence proposing the potential role of environmental factors, as well as genetic factors in the development of MS (13). Nonetheless, the marginal causal effect (i.e., the average causal effect in the total population) of waterpipe smoking, as a potential modifiable risk factor, on MS onset in Iran as well as the other settings has not been studied (14). To evaluate the marginal causal effect in case-control studies, there are several methodological strategies available but they have not been yet widely implemented in epidemiological studies (15-19). For example, inverse probability-of-treatment weighting (IPTW) using propensity scores (PS) (18, 20-24) and model-based standardization with the total population as the standard (15, 16, 20, 21, 25, 26) have been previously used for estimating marginal causal effects in case-control studies. While model-based standardization (MBS), also known as the parametric g-formula, has been introduced in cohort studies (27), it can be easily generalized to case-control studies if case and control sampling fractions are known (15, 20). However, Targeted Maximum Likelihood Estimation (TMLE) has been recently incorporated into the epidemiological methodological tools as one of the several methods of combining propensity score and parametric g-formula. It also includes a secondary targeting step that optimizes the bias-variance trade-off for the causal parameter of interest (28). TMLE is a preferred approach of estimating the marginal effects as it produces a double robust estimator. The reason is that either correct exposure or outcome model fitting would be sufficient for TMLE method to provide a valid estimate of parameter (16, 20, 29). In fact, TMLE has been shown to be robust against severe misspecification (e.g. omission of confounders) of either exposure or outcome model. Also TMLE is efficient if both exposure and outcome models are correct.

The authors have previously published an ordinary analysis of waterpipe smoking-MS association in this study population (30). Now, we want to reproduce findings using causal analysis. The aim of this study was to estimate a double-robust marginal causal effect of waterpipe smoking on MS using TMLE method in the setting of a population-based incident case-control study with known sampling fractions for both case and control groups.

METHODS

This was a population-based incident case-control study with all residents of 22 municipality areas of Tehran aged 15-50 years between August 7, 2013, and November 17, 2015 (nearly 5.11 million persons) as the study primary base (30, 31). We used the Iranian Multiple Sclerosis Society (IMSS), as the only registry in Tehran for recruitment of incident cases. Confirmed diagnosis of MS was established by at least one neurologist using 2010 McDonald criteria (32) as well as the use of magnetic resonance imaging (MRI). Index date was defined as the year and month in which the patients received their confirmed diagnosis. Using random digit dialing (RDD), we selected 1057 general population controls aged 15–50 years who were resident of the study base at the time of case diagnosis. The controls were selected proportional to size of 22 areas of Tehran. The study was approved by Research Ethics Committee of Tehran University of Medical Science with approval number of 26145.

RDD protocol- We used the standard method of RDD for identifying eligible controls (33). The existing codes of 22-areas were completed by four randomly generated digits. If the completed number was an active home landline phone number, the study interview was started; otherwise, the number was discarded. The similarity of selected controls using the RDD approach with that using address-based sampling (ABS) has been formerly shown (34). Moreover, its usefulness, effectiveness and feasibility had been previously demonstrated (33, 35, 36). Based on our RDD protocol, to identify and select potential controls, a maximum of 9 calls (2 times in a.m., 2 times in p.m. and 5 times in the different times of the other days) were made before a randomly generated number could be discarded. We excluded office phone numbers and finally reached a total of 1601 home numbers during the RDD process (approximately 35.9% of the generated random digits corresponded to home phone lines).To determine whether any household member met the study criteria, a screening interview was conducted before the study main interview during the same call. We applied the Kish method for random selection of eligible members of each selected household (37, 38).

Data collection- The phone interviews were conducted by 10 interviewers, selected for their strong communication and interview skills, and trained to use the standardized data collection procedures. The required information was identically extracted from both study groups.

Exposure- Participants were asked about the exposure, defined as lifetime waterpipe smoking for at least 1 time weekly during at least one 6-month period before the index date for cases or before the sampling date for controls. Given consumption in all weeks, those with a cumulative number of ≥24 times in a 6-month period were considered exposed; otherwise they were classified as unexposed.

Confounders- The selection of confounders was based on the causal directed acyclic graph (39-44) (Figure 2) through identifying a minimally sufficient adjustment set, and the following covariates were selected as confounders for the effect of waterpipe smoking on MS: Life style factors including cigarette pack-years, life-time history of any drug abuse (the use of illegal drugs for purposes other than those for which they are meant to be used), passive smoking history (yes/no), and lifetime alcohol consumption (gr), along with demographic factors i.e. age, gender and socioeconomic status (SES) as well as history of depression. We obtained the lifetime smoking behavior information before the index date in the cases and similarly during the same time in the controls. Information on duration (cumulative number of years of smoking) and intensity (average daily number of cigarettes smoked) of smoking were also acquired. Cigarette pack-years (number of years of smoking multiplied by average number of cigarettes smoked per day divided by 20) was then calculated based on the aforementioned data. One pack-year was defined as 20 cigarettes smoked per day for 1 year. Detailed information on lifetime alcohol consumption i.e. duration (year), average number of drinks per month and average drink size in each drink (ml) were obtained. Using this information, total lifetime ethanol (gr) was calculated through the University of Minnesota's nutrient data system (45, 46). Lifetime alcohol consumption (gr) for each source of alcohol (beer, wine and liquor) was separately calculated using the following formula for each source of alcoholic beverage:

Life-time alcohol consumption in gr = *received gr of specific alcoholic beverage in each drink* × *average number of drinks per month* × 12 × *duration (years).*

Then, total lifetime alcohol consumption (gr) was calculated as the sum of three lifetime specific alcoholic beverages. Lifetime history of any drug abuse for at least 1 time monthly during at least a 6-month period at the beginning of study was extracted via this question: Have you ever used any type of substance (Opioids, Cannabis, Inhalants, Hallucinogens and Stimulants) for at least 1 time monthly during at least a 6-month period? We measured passive smoking, as the other potential confounder, as the following: Have you ever lived in a home with someone who regularly smoked during your lifetime? Moreover, information on lifetime occurrence of depression was extracted through asking this question: Have you ever received depression diagnosis from a mental health professional during your lifetime? SES was measured using a 10 stairs ladder as a subjective visual scale (47). The data was extracted using the following instruction: "Imagine a ladder with 10 stairs representing where people stand in Tehran when they were adolescent (13-19-year old). At the top level of the ladder, there are those with the most money and the highest education and job situation. Reversely, at the bottom, there are those with the least money, and the poorest education and the worst job situations, i.e., the higher the stairs, the better the socio-economic status and vice versa. The participants were then requested to select the stair that best shows their SES in Tehran society (47). Collapsing the adjacent categories, the 10-item score of SES was transformed into 5 categories. Finally, information on demographic confounders was obtained in the case and control groups. The participants were requested to give all relevant information for the period before the index date for cases and before the sampling date for controls.

STATISTICAL METHODS

To estimate the case-control risk difference of waterpipe smoking on the onset of multiple sclerosis standardized to the distribution of the confounders, we first, applied the "Causal Roadmap" of Petersen and van der Laan (2014) (48) then estimate the risk difference, a.k.a average treatment effect, using a double-robust estimator namely the targeted maximum likelihood estimator (49). The following 5 TMLE steps were done to estimate the marginal causal effect of lifetime waterpipe smoking on multiple sclerosis:

i) We fitted an outcome logistic regression model with multiple sclerosis as outcome and waterpipe smoking and confounders as predictors.

ii) We also fitted the exposure model i.e. another logistic regression model with waterpipe smoking as outcome and confounders as predictors. Then the propensity score (PS) i.e. the probability of waterpipe smoking conditional on confounders was estimated.

iii) We calculated a weight variable H as $H = A/PS - ((1 - A)/(1 - PS))$ from the exposure model described in step (ii) where A is the exposure status (A=1 for exposed and A=0 for unexposed).

iv) To reduce the residual bias and optimize the bias-variance tradeoff for the risk difference estimate, we used information about the exposure mechanism in step (ii): we fitted an intercept-free outcome logistic regression model with multiple sclerosis as outcome, H as the predictor, and the right-hand side of the outcome regression model fitted in the step (i) as offset.

v) Finally, we calculated the standardized risk of MS in the waterpipe smokers (A=1) by predicting the individual risk of MS for the exposure forced to be 1 for all individuals, and actual values of confounders, and then averaging them over the individuals from the model fitted in step (iv). Similarly, we calculated the standardized risk of MS in the non-smokers (A=0) by predicting the individual risk for exposure forced to be 0 for all individuals, and actual values of confounders, and then averaging them over the individuals. Using the estimated standardized risk in the waterpipe smokers and nonsmokers, we calculated the effect measure of interest i.e. risk difference (RD), risk ratio (RR) and odds ratio (OR). It is important to note that the models mentioned in steps (i), (ii), and (iv) are fitted using inverse probability weighting with weights equal 1/(367/570)=1.55 for cases and 1/(990/(5115679-20000))= 5147.15 for controls (18, 50). This IPW takes into account sampling fraction of cases and controls as well as missing data.

The TMLE estimates enjoy some useful statistical properties including they are consistent as long as either outcome or exposure model is correctly specified, and if both models are correct the final estimate achieves its smallest possible variance as sample size approaches infinity (49). We also calculated the population attributable fraction (PAF) using the Miettinen formula i.e. PAF= [P(e=1)|(D=1)]×[(RR-1)/RR], where [P(e=1)|(D=1)] is the prevalence of waterpipe smoking in cases and RR is the risk ratio (51, 52).

Model specification- We used an ensemble machine learning approach, namely the "super learning" for exposure and outcome model specification. The approach is based on an optimal weighted linear combination of several machine learning algorithms including: Generalized Linear Model (GLM), Stepwise logistic regression (Step), Generalized Linear Model with considering interaction (glm.interaction), Generalized Additive Model (gam), Recursive Partitioning and Regression Trees (rpart), Lasso and Elastic-Net Regularized Generalized Linear Models (glmnet) (16). We used influence functions (49, 53) to calculate 95% confidence intervals for RR, OR, RD, and PAF. All statistical analyses were done using the statistical software R (R foundation for statistical computing, Vienna, Austria) and the R package (LTMLE) (54) We provide the code used for analysis as supplementary file for reproducibility (Supplementary File 1).

RESULTS

During the 1.5-year study period, we identified 570 newly diagnosed MS patients. Of them, 547(96.0%) accepted to participate in our case-control study. In the end of the RDD process, 2856 (64.1%) of 4457 random generated digits were inactive or office phone numbers or not available. Of active ones, we could not persuade 453 households to participate in our study. While 128 (28.3%) of these households did not agree to respond to the study screening interview, we could not convince 325 (71.7%) of them, after description of study goals, to participate in the study. Also 91 households did not have eligible 15-50 years old individuals. Overall, 1057 (70.0%) of eligible random digit numbers have been included as study controls and completed the main study checklist (Response rate: 70.0%) (Figure 1).

Of 547 incident cases, about 483 (88.3%) were <40 years old at the time of diagnosis. While, 166 (30.4%) of cases reported lifetime waterpipe smoking for at least 1 time weekly during at least 6-month period, 252 (23.9%) of controls reported a similar experience. Similarly, drug abuse history was reported in 11.4% of cases and 6.6% of controls, respectively.

As shown in Table 1, the prevalence of drug abuse, passive smoking, life-time alcohol consumption as well as depression and female gender were importantly greater in cases than control groups.

The estimated marginal effects of waterpipe smoking on MS using TMLE and super learning in the term of ratio and difference measures i.e. RR, OR, and RD are presented in Table 2. The estimated RD of waterpipe smoking was 6.80 per 100,000, 95% CI: (3.50, 10.20). The estimated OR was the same with RR: 1.70, 95% CI: (1.34, 2.17), P <0.001, showing a higher odds and risk of MS for those who were waterpipe smoker. The PAF estimate was 21.4% (95% CI: 4.0%, 38.8%) (Table 2). However, a similar point estimate for PAF with moderately narrower confidence interval was found based on bootstrap approach without data adaptive estimation: 21.4% (95% CI: 17.6%, 33.6%).

DISCUSSION

Using the double-robust TMLE, lifetime waterpipe smoking for at least 1 time weekly during at least a 6-month period increased the onset risk of MS by 70% compared to non-waterpipe smokers. Given the rarity of the outcome in the population, both RR and OR were similar. In line with conditional analysis previously reported (30), the estimated RR and OR in marginal analysis add summative evidence to the role of waterpipe smoking as an independent risk factor for MS. The potential causal link between waterpipe use and MS can be explained by existent neurotoxic components e.g. lead and carbon monoxide in the waterpipe smoke composition (55). We also found that waterpipe smoking or its strongly related but undetermined factors, is responsible for around 21.4% (95% CI: 4.0%, 38.8%) of MS incidence in the population level which is somewhat larger than our previous estimate (17%) using classical methods (i.e. logistic regression) (30). Apart from different analysis approaches, the estimated marginal effect of waterpipe smoking in this study was further adjusted for tobacco and passive smoking, SES, depression, as well as lifetime drug abuse and alcohol consumption using the causal diagram in Figure 2.

The target of our effect estimate was total population as the standard TMLE generally estimates average treatment effect (ATE) (28). It is important to note that ATE and average treatment effect in the treated (ATT) would diverge only in the presence of substantial non-uniform effects (56).

TMLE employs an algorithm which produces valid estimates if either outcome or exposure model is correct. Using supper learner approach in TMLE decreases the possibility of model misspecification (57). Compared to either g-formula or IPTW, an additional strength of TMLE is that it can be combined with machine learning without affecting the statistical properties of the estimator (58).

Our results should be interpreted with some limitations in mind. With all causal analyses including those used in this paper, it is only expected to remove the effect of measured, but not unknown or unmeasured confounders. Therefore, unmeasured and unknown covariates can still be imbalanced between waterpipe users and non-users leading to residual confounding. Also there were measurement error in the waterpipe smoking (due to a simplified definition of exposure), recall bias, and underreporting bias leading to measurement bias. It seems that due to the life-style nature of the exposure (and confounders), the magnitude of distortion resulted from recall bias is not substantial, and as mentioned in our previous paper (30), waterpipe smoking is not a social stigma in Iranian society, reducing the possibility of underreporting bias. Moreover, measurement error in confounders including drug abuse and alcohol intake may result in residual confounding. However, the direction and magnitude of imposed bias due to measurement error of exposure and confounders are not predictable without knowledge of errors structure (15, 59, 60). The possibility of selection bias is another issue threatening the validity of the findings of this study. RDD can access only a subset of home phone lines and cannot reach those households without an active telephone line, which implies a stable residence and a certain income level, leading to selection bias. However, the response rate for cases was 96%. This could alleviate the possibility of selection bias in case group. Although, the response rate in the control group was significantly smaller than for cases, compared with other studies, this may be considered as a satisfactory response rate (61). We did not have data on body mass index as the formerly identified risk factor on MS. Waterpipe can be used for smoking cannabis and tobacco as well, but, there was not the possibility of differentiating the type of material smoked in each session of waterpipe smoking. Thus, we really isolated the effect of the methods of smoking. Finally, double-robust methods are not efficient if both exposure and outcome models are missspecified (62).

In summary, based on the results of the study, we conclude that lifetime waterpipe smoking for at least 1 time weekly during at least 6-month period, as a modifiable risk factor, could significantly increase the risk of MS in Tehran. Therefore, we urge the development of public health educational programs aiming at reducing the use of waterpipe smoking given the evidence of an increased risk of developing MS among smokers. Tackling the threatening waterpipe use epidemic may be useful in decreasing new cases of MS in Tehran during the coming years. Further epidemiological studies e.g. nested case-control studies are needed to confirm the results.

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Table 1. Demographic characteristics of multiple sclerosis cases and controls, Tehran, 2013-2015

Characteristic	Multiple sclerosis cases (n=547)		Controls (n=1057)	
	n	(%)	n	(%)
Life-time waterpipe smoking≥24 times				
Yes	166	30.4	252	23.9
Marriage				
Single	246	45.1	486	46.2
Married	300	54.9	567	53.8
Gender				
Female	401	73.3	544	51.5
Age (years)[a]	30.5 (7.53)		31.3 (9.33)	
SES (1-5)[a]	3.14 (1.03)		3.27 (0.99)	
Cigarette Pack-year				
Never	438	80.2	843	80.0
≤ 5	79	14.5	165	15.7
> 5	29	5.3	46	4.4
Lifetime alcohol consumption				
Never	394	72.8	805	77.6
≤ 1000 gr	58	10.7	66	6.4
> 1000 gr	89	16.5	167	16.1
Drug abuse				
Yes	64	11.7	71	6.7
Passive Smoking				
Yes	285	52.2	390	37.0

Depression				
Yes	197	36	170	16.1

SES: socio-economic status

[a] mean (standard deviation)

Table 2. The estimated marginal causal effect and potential impact of waterpipe smoking on MS using TMLE method and super learning, Tehran, 2013-2015

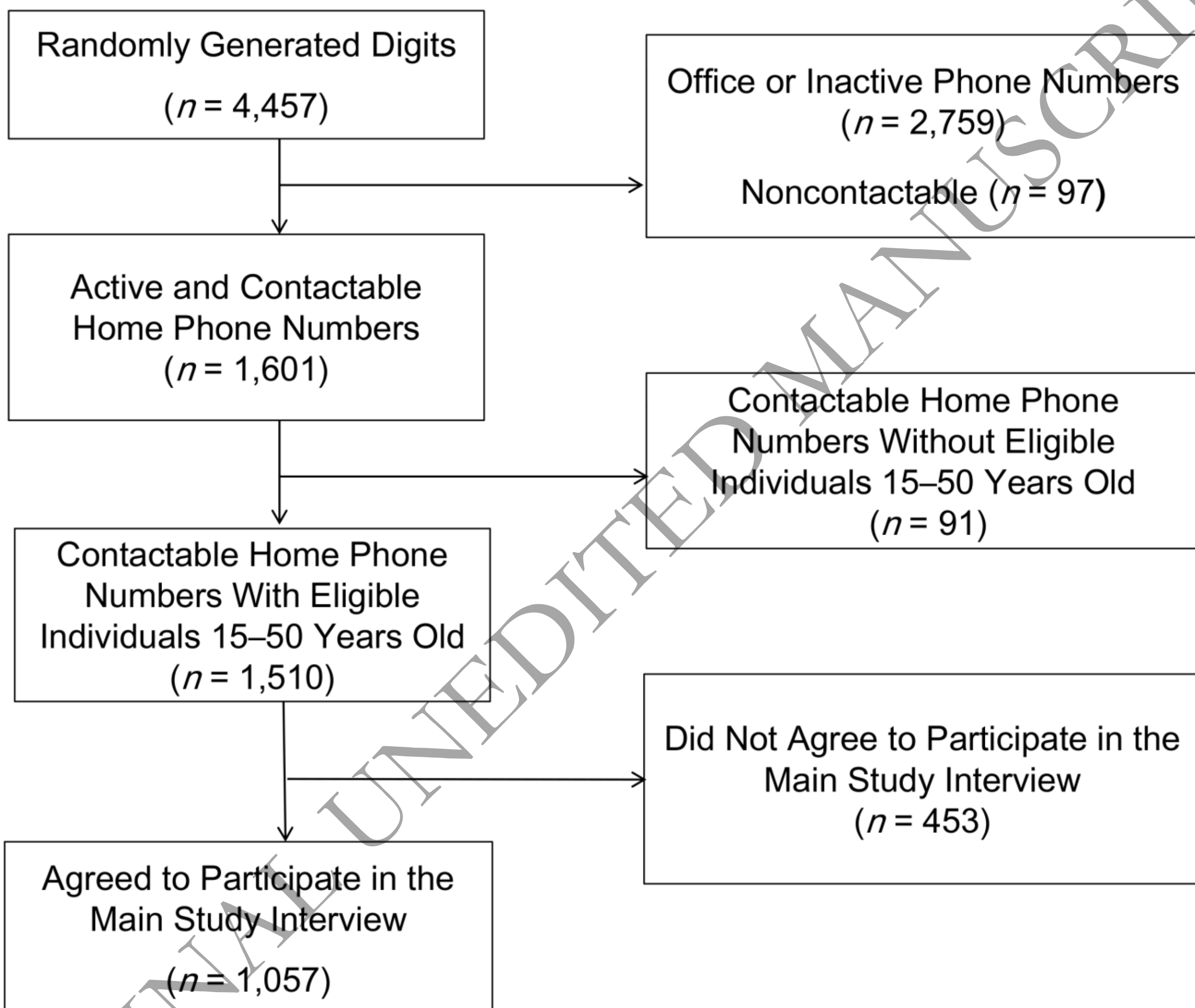
	Causal effect/potential impact										
Causal method	RR	95% CI	P Value	OR	95% CI	P Value	RD	95% CI	P Value	PAR	95% CI
TMLE Using Super Learning	1.70	1.34, 2.17	<0.001	1.7	1.34, 2.17	<0.001	6.80[a]	3.50, 10.20	<0.001	21.4	4.0, 38.8

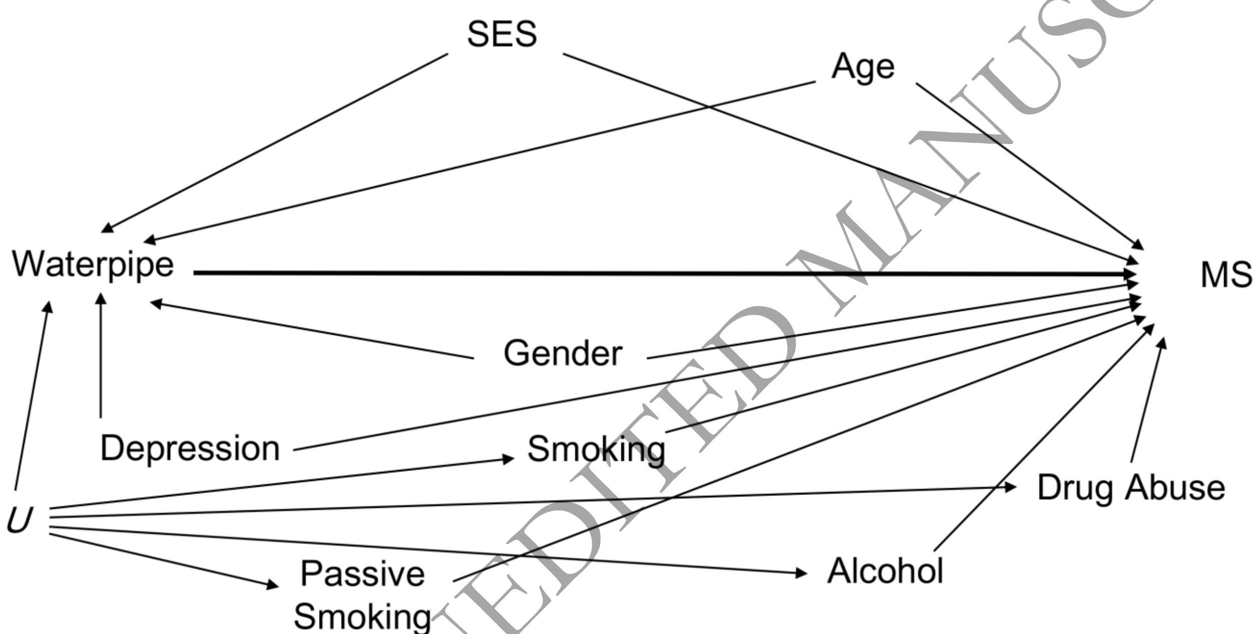
RR: risk ratio; OR: odds ratio; RD: risk difference; PAF: population attributable fraction; CI: confidence interval

[a] Per 100,000

Figure 1. Recruitment flowchart of general population controls in Tehran, 2013-2015

Figure 2. A causal diagram representing the effect of waterpipe smoking on multiple sclerosis (MS); U represents unmeasured covariates such as personality traits (To avoid clutter and without loss of validity of backdoor criterion, the arrows between confounders have not been shown); SES: socio-economic status


Randomly Generated Digits
(n = 4,457)
Office or Inactive Phone Numbers
(n = 2,759)
Noncontactable (n = 97)
Active and Contactable
Home Phone Numbers
(n = 1,601)
Contactable Home Phone
Numbers Without Eligible
Individuals 15–50 Years Old
(n = 91)
Contactable Home Phone
Numbers With Eligible
Individuals 15–50 Years Old
(n = 1,510)
Did Not Agree to Participate in the
Main Study Interview
(n = 453)
Agreed to Participate in the
Main Study Interview
(n = 1,057)


SES
Age
Waterpipe
MS
Gender
Depression
Smoking
Drug Abuse
U
Passive
Smoking
Alcohol