Journal of Diabetes and Its Complications 29 (2015) 1032–1036

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Serum cotinine levels and diabetes mellitus in never smokers

Omayma Alshaarawy [a,*], Hosam A. Elbaz [b]

[a] Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI 48823, United States
[b] Department of Internal Medicine, Division of Gastroenterology, University of Michigan, Ann Arbor, MI 48109, United States

ARTICLE INFO

Article history:
Received 22 June 2015
Received in revised form 20 August 2015
Accepted 21 August 2015
Available online 24 August 2015

Keywords:
Environmental tobacco smoke
NHANES
Diabetes mellitus
Cotinine
Never smokers
Meta-analysis

ABSTRACT

Objective: The aim of the current study is to examine the association of environmental tobacco smoke (ETS) exposure evident by serum cotinine level, and diabetes mellitus in never smokers. Previous studies suggest that active tobacco cigarette smoking is associated with diabetes mellitus risk. However it is not clear if the low-level "background" ETS exposure is associated with diabetes among never smokers.
Methods: We present evidence from five independent replications based on the US nationally representative National Health and Nutrition Examination Surveys (NHANES) conducted 2003–12. Our exposure of interest is ETS exposure among never smokers, measured by serum cotinine levels (ng/mL), and our main outcome is diabetes mellitus assessed via self-reported physician-diagnosis, current use of insulin and/or oral hypoglycemic medications, plasma fasting glucose levels ≥126 mg/dL or glycohemoglobin levels ≥6.5%. The conceptual model encompassed age, sex, ethnic self-identification, education, poverty-income ratio, alcohol drinking, total cholesterol and body mass index.
Results: In never smokers, higher serum cotinine levels were positively associated with diabetes mellitus (the meta-analytic summary estimate is 1.2, 95% CI = 1.1, 1.2). This association was not evident among never smokers with cotinine levels below 3 ng/mL.
Conclusions: These replications help sustain evidence of ETS–diabetes mellitus association, which might be explained by shared psychosocial characteristics. Prospective studies with appropriate biomarkers are needed to further investigate this association.

1. Introduction

Several studies suggest that tobacco cigarette smoking is associated with an increased risk of developing type 2 diabetes mellitus among active smokers (Willi, Bodenmann, Ghali, Faris, & Cornuz, 2007). There are only few studies investigating the relationship between environmental tobacco smoke (ETS) exposure and diabetes in never smokers (Wang, Ji, Liu, Deng, & He, 2013), but this relationship might be biased if smokers do not accurately report their smoking status (Fisher, Taylor, Shelton, & Debanne, 2007). Cotinine, the principal metabolite of nicotine, is considered a more precise measure of exposure to cigarette smoking when compared to self-reported smoking status (Benowitz, 1996; Gorber, Schofield-Hurwitz, Hardt, Levasseur, & Tremblay, 2009). Houston et al. (2006) used serum cotinine to validate smoking status in a 15-year biracial cohort of United States (US) adults and found that people with exposure to ETS; defined as participants who self-reported being never smokers and exposed to ETS, or had cotinine concentrations of 1–15 ng/mL, had an intermediate risk of developing diabetes between current smokers and never smokers without ETS exposure. However, this study only represents African-Americans and Whites recruited from four urban areas in the US and hence the results are not necessarily generalizable to other populations.

The number of states with comprehensive smoke-free laws in effect increased from zero on 2000, to 26 states on 2010. Between 2004 and 2007, an increasing number of states enacted different smoke-free laws that prohibit smoking in workplaces and public areas (United States Centers for Disease Control and Prevention, 2011). Accordingly exposure to ETS has steadily decreased in the US over time evident by cotinine concentrations (United States Centers for Disease Control and Prevention, 2010a, 2010b). The cotinine cutpoint of 15 ng/mL widely used in previous research to differentiate smokers from non-smokers was determined by Jarvis, Tunstall-Pedoe, Feyerabend, Vesey, and Saloojee (1987) more than 27 years ago when no or less strict public smoking regulations have been placed. Benowitz, Bernert, Caraballo, Holiday, and Wang (2009) recently suggested a lower cotinine cutpoints of 3.0 ng/mL to differentiate non-smokers from smokers, whereas levels >3 ng/mL might reflect heavier exposure to ETS or mis-reported smoking status. On the other hand, analyses of nationally representative data from 1980 to 2012 suggest a doubling of the incidence of diabetes during 1990–2008, and a plateauing between 2008 and 2012 (Geiss et al., 2014).

Conflict of interest: There is no conflict of interest to disclose.

* Corresponding author at: Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI 48823, United States. Tel.: +1 517 353 8623.
E-mail address: oalshaarawy@epi.msu.edu (O. Alshaarawy).

http://dx.doi.org/10.1016/j.jdiacomp.2015.08.018
1056-8727/

The aim of the current study is to investigate the association of ETS evident by serum cotinine levels and diabetes mellitus in never smokers. We derive estimates from the US nationally representative sample surveys with standardized methods; the National Health and Nutrition Examination Survey (NHANES) 2003–04, 2005–06, 2007–08, 2009–10 and 2011–12. We use a meta-analysis approach treating each data-cycle's independent sample as a separate study and deriving estimates from multiple independent replication samples (DeAndrea et al., 2013).

2. Methods

2.1. Study population: never smokers ≥20 years of age

Each NHANES replication is designed to yield nationally representative sample survey estimates for the US non-institutionalized civilian population through multistage area probability sampling. NHANES replication estimates can be derived by combining survey cycles as follows: 2003–04, 2005–6; 2007–8; 2009–10; and 2011–12. The within-cycle analysis weights take into account specific subgroups that are over-sampled in order to increase precision of NHANES estimates, as well as post-stratification adjustments (United States Centers for Disease Control and Prevention, 2010a, 2010b). Fig. 1 presents a flow chart describing the study methodology and sample population. The NHANES study protocol has been reviewed and approved by cognizant institutional review boards for protection of human subjects in research.

2.2. Study outcome

The key response variable in this study is diabetes mellitus. In NHANES, diabetes mellitus is assessed based on a respondent-reported physician-diagnosis through the question "Other than during pregnancy have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?" NHANES also has questions on current use of insulin and/or oral hypoglycemic medicines in addition to plasma fasting glucose and glycosylated hemoglobin (HbA1c) level measurement summarized in relation to American Diabetes Association guidelines for fasting glucose ≥126 mg/dL and HbA1c ≥6.5% (American Diabetes Association, 2010).

Fasting plasma glucose was tested in a subsample of NHANES participants who were examined in the morning session. Glycohemoglobin measures are available for the full sample. Glucose was analyzed using an enzymatic method where it is converted to glucose-6-phosphate (G-6-P) by hexokinase in the presence of adenosine triphosphate, a phosphate donor. Glucose-6-phosphate dehydrogenase then converts the G-6-P to gluconate-6-P in the presence of nicotinamide adenine dinucleotide (NADP+). As the NADP+ is reduced to NADPH during this reaction, the resulting increase in absorbance at 340 nm (secondary wavelength = 700 nm) is measured. This is an endpoint reaction that is specific for glucose.

In NHANES 2003–06, HbA1c was measured on the A1c 2.2 Plus Glycohemoglobin Analyzer (Tosoh Medics, Inc., 347 Oyster Pt. Blvd., Suite 201, So., San Francisco, CA 94080) whereas in NHANES 2007–12, HbA1c was measured on the A1c G7 HPLC Glycohemoglobin Analyzer (Tosoh Medics, Inc., 347 Oyster Pt. Blvd., Suite 201, So. San Francisco, CA 94080) (United States Centers for Disease Control and Prevention, 2006).

2.3. Study exposure

The covariate of central interest is serum cotinine levels (ng/mL) in never smokers. Serum cotinine was measured by an isotope dilution–high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry (ID HPLC-APCI MS/MS). Cotinine concentrations were derived from the ratio of native/labeled cotinine in the sample, by comparisons to a standard curve. Detailed description of serum cotinine measurement in NHANES is available online (United States Centers for Disease Control and Prevention, 2006).

The standardized smoking questionnaire was administered in the household interview using the Computer-Assisted Personal Interviewing system (interviewer administered). On this basis, participants can be classified as never smokers; past smokers (smoked at least 100 cigarettes in lifetime and currently not smoking); and recently active smokers (smoked at least 100 cigarettes in lifetime and currently smoking). Never smokers with serum cotinine level >15 ng/mL which might reflect misclassification of smoking status were not included in the current analyses. Nicotine can be absorbed from other forms of tobacco and

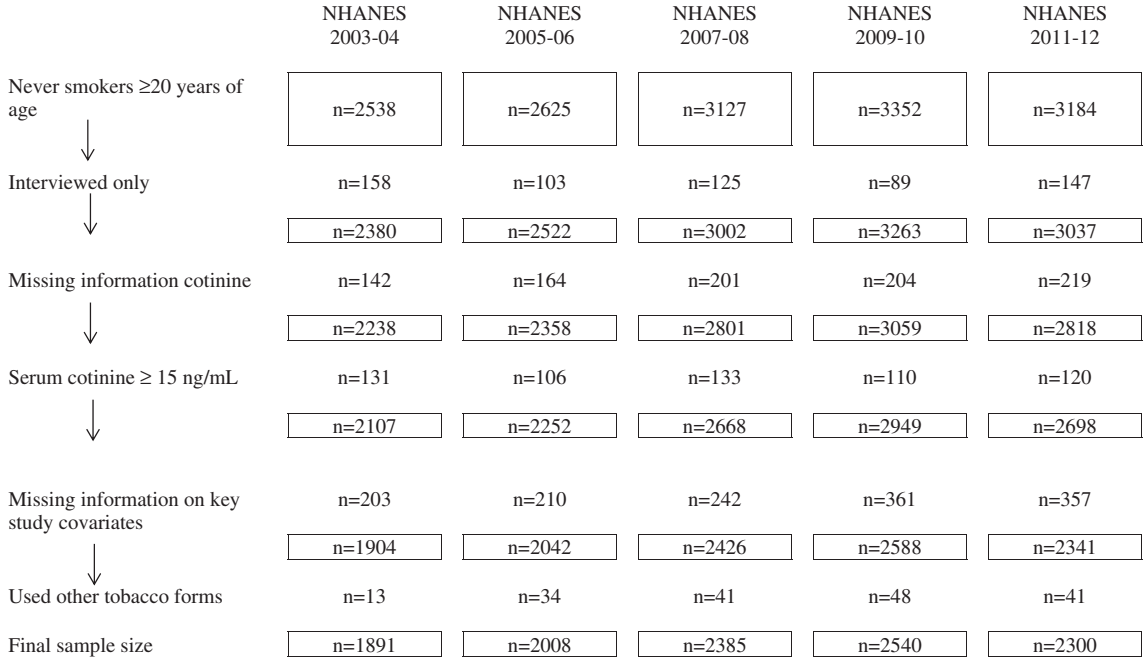

Fig. 1. Flowchart describing the study methodology and sample population for each independent replication sample. Data for the United States based on the National Health and Nutrition Examination Survey, 2003–2012.