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REFERENCES

1. Kumanovics A, Lee YN, Close DW, Coonrod EM, Ujhazi B, Chen K, et al. Estimated disease incidence of RAG1/2 mutations: a case report and querying the Exome Aggregation Consortium. *J Allergy Clin Immunol* 2017;139:690-2.e3.
2. Kwan A, Abraham RS, Currier R, Brower A, Andruszewski K, Abbott JK, et al. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. *JAMA* 2014;312:729-38.
3. Schwarz K, Gauss GH, Ludwig L, Pannicke U, Li Z, Lindner D, et al. RAG mutations in human B cell-negative SCID. *Science* 1996;274:97-9.
4. Felgentreff K, Perez-Becker R, Speckmann C, Schwarz K, Kalwak K, Markelj G, et al. Clinical and immunological manifestations of patients with atypical severe combined immunodeficiency. *Clin Immunol* 2011;141:73-82.
5. Walter JE, Rosen LB, Csomos K, Rosenberg JM, Mathew D, Keszei M, et al. Broad-spectrum antibodies against self-antigens and cytokines in RAG deficiency. *J Clin Invest* 2015;125:4135-48.
6. Buchbinder D, Baker R, Lee YN, Ravell J, Zhang Y, McElwee J, et al. Identification of patients with RAG mutations previously diagnosed with common variable immunodeficiency disorders. *J Clin Immunol* 2015;35:119-24.
7. Geier CB, Piller A, Linder A, Sauerwein KM, Eibl MM, Wolf HM. Leaky RAG deficiency in adult patients with impaired antibody production against bacterial polysaccharide antigens. *PLoS One* 2015;10:e0133220.
8. Tuijnburg P, Lango Allen H, Burns SO, Greene D, Jansen MH, Staples E, et al. Loss of function NFKB1 variants are the most common monogenic cause of CVID in Europeans. *J Allergy Clin Immunol* 2018 Feb 22. <http://dx.doi.org/10.1016/j.jaci.2018.01.039> [Epub ahead of print].
9. Lee YN, Frugoni F, Dobbs K, Walter JE, Giliani S, Gennery AR, et al. A systematic analysis of recombination activity and genotype-phenotype correlation in human recombination-activating gene 1 deficiency. *J Allergy Clin Immunol* 2014;133:1099-108.
10. Speckmann C, Doerken S, Aiuti A, Albert MH, Al-Herz W, Allende LM, et al. A prospective study on the natural history of patients with profound combined immunodeficiency: an interim analysis. *J Allergy Clin Immunol* 2017;139:1302-10.e4.

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Proximity to traffic and asthma among Mexican American children: Independent and interactive effects



To the Editor:

Studies linking proximity to traffic, a surrogate measure of exposure to traffic-related air pollution (TRAP), with an increased risk of respiratory conditions in children have produced

inconsistent findings. Some studies showed positive associations of TRAP with asthma and wheezing in children with a family history of asthma or allergies,^{1,2} whereas other investigations^{3,4} found positive associations only in children without parental history of atopic conditions. In the United States, there is evidence demonstrating that racial/ethnic minority populations including Mexican Americans (MAs) are more likely to live near major roads or reside in neighborhoods with increased traffic and therefore experience a disproportionate share of air pollution exposure. However, MAs remain underrepresented in research on the role of TRAP in the etiology of respiratory disease. In this study, we tested associations of proximity to traffic with childhood respiratory outcomes (lifetime asthma, lifetime wheezing, and current wheezing) and whether these associations differed by parental history of asthma or allergies, individual-level sociodemographic characteristics, immigration-related factors, and environmental stressors.

Details of the research methodology are provided in this article's [Methods](#) section in the Online Repository at www.jacionline.org. Briefly, individual-level data were collected as part of the Study of Asthma in Children of Mexican Descent, a population-based, cross-sectional study.⁵ Between August 2004 and April 2005, the parents of 2023 children (grades K-8) completed a mailed questionnaire or telephone interview about respiratory conditions and factors related to asthma in their children. We geocoded the addresses of all children using geographic information system software. The locations of all primary arterials were obtained from the Illinois Department of Transportation for the year 2004. Proximity to traffic was examined as a 4-level (0-150 m; 151-250 m; 251-500 m; >500 m) and a binary (0-250 m; >250 m) variable. The study outcomes include parent report of lifetime asthma, lifetime wheezing (wheezing or whistling), and current wheezing (in the last 12 months). The final analysis was based on data for 1925 children with complete data. The current analysis was approved by the Institutional Review Board of the University of Illinois at Chicago.

We performed multilevel logistic regression analyses using generalized estimating equations to estimate the odds ratio (OR) for the association of proximity to traffic with respiratory outcomes. In separate analyses, we examined interactions between the binary traffic-related exposure variable and potential moderators. All models accounted for clustering of children within neighborhoods.

Of the 1925 participants, 6.7%, 17.0%, and 6.0% had lifetime asthma, lifetime wheezing, and current wheezing, respectively, and 7.8% had parental history of asthma or allergies. In fully adjusted multilevel logistic regression analyses treating proximity to traffic as a 4-level variable, the odds of lifetime asthma were greater among children who lived between 0 and 150 m (OR, 2.39; 95% CI, 1.39-4.10) and 151 to 250 m (OR, 2.37; 95% CI, 1.34, 4.19) relative to those who lived more than 500 m from a primary traffic arterial ([Table 1](#)). When we examined proximity to traffic as a binary exposure, the odds of lifetime asthma (OR, 2.21; 95% CI, 1.50-3.25) and lifetime wheezing (OR, 1.52; 95% CI, 1.17-1.97) were significantly higher for children who lived 0 to 250 m compared with those who lived more than 250 m from primary traffic arterials ([Table 1](#)).

The associations of proximity to primary traffic arterials with lifetime asthma and lifetime wheezing, but not current wheezing, were modified by parental history of asthma or allergies (*P* for

TABLE I. Crude and adjusted associations of proximity to primary traffic arterials with asthma and asthma-related symptoms

Outcome variables*	Proximity to primary traffic arterials (4 levels)				Proximity to primary traffic arterials (binary)	
	0-150 m†	151-250 m†	251-500 m†	>500 m	0-250 m†	>250 m
Lifetime asthma						
Crude	2.22‡ (1.20-4.08)	2.38‡ (1.41-4.03)	1.28 (0.76-2.15)	1.00	2.19‡ (1.55-3.09)	1.00
Partially adjusted	2.34‡ (1.36-4.02)	2.34‡ (1.34-4.08)	1.36 (0.78-2.37)	1.00	2.18‡ (1.50-3.16)	1.00
Fully adjusted	2.39‡ (1.39-4.10)	2.37‡ (1.34-4.19)	1.34 (0.77-2.32)	1.00	2.21‡ (1.50-3.25)	1.00
Lifetime wheezing						
Crude	1.56 (0.95-2.59)	1.49‡ (1.03-2.16)	1.07 (0.79-1.47)	1.00	1.51‡ (1.19-1.93)	1.00
Partially adjusted	1.55 (0.96-2.50)	1.48‡ (1.10-2.00)	1.11 (0.82-1.50)	1.00	1.50‡ (1.17-1.91)	1.00
Fully adjusted	1.58 (0.96-2.59)	1.48‡ (1.09-1.99)	1.07 (0.79-1.44)	1.00	1.52‡ (1.17-1.97)	1.00
Current wheezing						
Crude	1.42 (0.81-2.51)	1.62 (0.89-2.95)	1.28 (0.75-2.17)	1.00	1.42 (0.93-2.18)	1.00
Partially adjusted	1.41 (0.79-2.50)	1.70 (0.94-3.06)	1.29 (0.76-2.20)	1.00	1.46 (0.96-2.22)	1.00
Fully adjusted	1.47 (0.83-2.60)	1.74 (0.95-3.18)	1.30 (0.77-2.20)	1.00	1.51 (0.99-2.30)	1.00

*Partially adjusted model: adjusted for age, sex, country of birth, day-care or preschool attendance, access to a regular doctor or clinic, parental history of asthma or allergies, smoker present at home at the time of child's birth, viral infection in the first year of life, and ear infection in the first year of life. Fully adjusted model: additionally adjusted for standardized percent of residents who state they are of Mexican origin, standardized population density, standardized total number of crimes reported for 2004, and composite index of neighborhood deprivation.

†Values are OR (95% CI).

‡ $P < .05$.

TABLE II. Stratified adjusted* association of proximity to primary traffic arterials (0-250 m vs >250 m) with lifetime asthma and lifetime wheezing

Variable	OR (95% CI)	
	Lifetime asthma	Lifetime wheezing
Proximity to primary traffic arterials (0-250 m vs >250 m)†‡		
No parental history of asthma or allergies	1.71§ (1.13-2.59)	1.24 (0.94-1.64)
Positive parental history of asthma or allergies	8.67§ (3.18-23.62)	8.28§ (2.64-25.96)

*Model is adjusted for age, sex, country of birth, day-care or preschool attendance, access to a regular doctor or clinic, smoker present at home at the time of child's birth, viral infection in the first year of life, ear infection in the first year of life, standardized percent of residents who state they are of Mexican origin, standardized population density, standardized total number of crimes reported for 2004, and composite index of neighborhood deprivation.

†Significant interaction between proximity to traffic and parental history of asthma or allergies.

‡ORs and 95% CI calculated from the final multivariable logistic regression model with an interaction term between proximity to primary traffic arterials (0-250 m vs >250 m) and parental history of asthma or allergies (yes vs no).

§ $P < .05$.

interaction = .01 for both). Compared with children living more than 250 m, those living 0 to 250 m from primary traffic arterials had a more than 8-fold increase in the odds of lifetime asthma (OR, 8.67; 95% CI, 3.18-23.62) and lifetime wheezing (OR, 8.28; 95% CI, 2.64-25.96) if they also had a positive parental history of asthma or allergies (Table II). In the absence of parental history of asthma or allergies, the odds of lifetime asthma and lifetime wheezing were much attenuated or null for children living 0 to 250 m from primary traffic arterials (Table II). We did not observe statistically significant interactions between proximity to traffic and child's sex, country of birth, length of residence in the United States (for Mexico-born children), perinatal exposure to environmental tobacco smoke, neighborhood deprivation, or neighborhood crime.

The odds of current wheezing in children who lived within 150 or 250 m from primary traffic arterials were elevated but did not reach statistical significance, perhaps a result of smaller numbers of children currently wheezing compared with lifetime wheezing (6% vs 17%). For instance, the ORs (Table I) for those living 151 to 250 m versus more than 500 m were higher for current wheezing than for lifetime wheezing with CIs that are somewhat larger.

The finding that living within 250 m (vs >250 m) of primary traffic arterials was independently associated with elevated odds of lifetime asthma and lifetime wheezing adds to the previous literature showing a negative impact of residential or school proximity to traffic on respiratory outcomes in children.^{1-4,6,7} The distances at which an increased risk of asthma and respiratory symptoms was noted in previous studies were not consistent and generally varied from 50 m to 300 m, with studies showing that the risk decreases to background levels by 150 to 300 m from major roadways.^{6,7} In our study, the increased risks associated with living within 150 or within 151 to 250 m from primary traffic arterials were similar but different from the risk associated with living more than 250 m from primary traffic arterials. Therefore, we combined the 2 levels in our final analysis. Because of sample size limitations, we were not able to reliably assess the impact of living within smaller distances from major roads. As reviewed in Karner et al,⁸ several factors such as traffic conditions and wind speed, as well as direction, affect near-road pollutant concentrations. In addition, concentrations of most traffic-related pollutants decline to background levels between 160 and 570 m based on background normalization, with benzene, nitrogen dioxide, and elemental carbon decreasing to background levels after 280, 380, and 420 m, respectively.⁸

Consistent with some,^{1,2} but not all,^{3,4} previous investigations, we found that the associations of proximity to traffic with lifetime asthma and lifetime wheezing were more profound in children with parental history of asthma or allergies. This is congruent with evidence suggesting that the adverse effects of exposure to TRAP on the risk of asthma

and asthma-related respiratory symptoms vary on the basis of factors that may increase susceptibility to the negative effect of TRAP.^{4,7,9} For example, a recent review⁹ suggested that the detrimental effect of TRAP exposure on the risk of respiratory conditions was limited to children with history of allergies and demonstrated synergistic effects between TRAP exposure and low socioeconomic status, exposure to high levels of violence, and high parental stress.

Although biologically plausible, our findings must be interpreted with caution due to the cross-sectional design of this study and potential confounding by unmeasured factors such as aeroallergen sensitivities. Furthermore, we did not have direct measures of air pollution in this study. In this study, we relied on neighborhood data based on the child's address at the time of the survey and had no data on the child's address early in life or length of time at the residence at the time of survey. Nonetheless, our findings add to mounting evidence demonstrating the important role of place-based health inequities, and, in particular, proximity to traffic on respiratory health among MA children.

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REFERENCES

1. Carlsten C, Dybuncio A, Becker A, Chan-Yeung M, Brauer M. Traffic-related air pollution and incident asthma in a high-risk birth cohort. *Occup Environ Med* 2011;68:291-5.
2. Ryan PH, LeMasters G, Biagini J, Bernstein D, Grinshpun SA, Shukla R, et al. Is it traffic type, volume, or distance? Wheezing in infants living near truck and bus traffic. *J Allergy Clin Immunol* 2005;116:279-84.
3. Gordian ME, Haneuse S, Wakefield J. An investigation of the association between traffic exposure and the diagnosis of asthma in children. *J Expo Sci Environ Epidemiol* 2006;16:49-55.
4. McConnell R, Berhane K, Yao L, Jerrett M, Lurmann F, Gilliland F, et al. Traffic, susceptibility, and childhood asthma. *Environ Health Perspect* 2006;114:766-72.
5. Eldeirawi K, McConnell R, Furner S, Freels S, Stayner L, Hernandez E, et al. Associations of doctor-diagnosed asthma with immigration status, age at immigration, and length of residence in the United States in a sample of Mexican American school children in Chicago. *J Asthma* 2009;46:796-802.
6. Bowatte G, Lodge C, Lowe AJ, Erbas B, Perret J, Abramson MJ, et al. The influence of childhood traffic-related air pollution exposure on asthma, allergy and

sensitization: a systematic review and a meta-analysis of birth cohort studies. *Allergy* 2015;70:245-56.

7. Salam MT, Islam T, Gilliland FD. Recent evidence for adverse effects of residential proximity to traffic sources on asthma. *Curr Opin Pulm Med* 2008;14:3-8.
8. Karner AA, Eisinger DS, Niemeier DA. Near-roadway air quality: synthesizing the findings from real-world data. *Environ Sci Technol* 2010;44:5334-44.
9. Burte E, Nadif R, Jacquemin B. Susceptibility factors relevant for the association between long-term air pollution exposure and incident asthma. *Curr Environ Health Rep* 2016;3:23-39.

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CD40LG duplication-associated autoimmune disease is silenced by nonrandom X-chromosome inactivation



To the Editor:

Gene duplication expands genome size and is the initial step in paralog formation. Not all gene duplication events are immediately beneficial; some result in functional disomy and convey a survival disadvantage until silenced.¹ On an autosome, gene silencing requires the random accumulation of loss-of-function mutations, but on a sex chromosome, females can rapidly silence disadvantageous alleles via nonrandom X-chromosome inactivation (XCI).² It has been proposed that reactivation of sex-linked, immune-related genes may contribute to the observed female bias of autoimmune diseases.^{3,4}

The X-linked gene *CD40LG* encodes CD40L, a T-cell coactivation receptor expressed under transcriptional control of nuclear factor of activated T cells.⁵ CD40L-deficient patients display impaired immunoglobulin class-switching and defective cellular immunity, whereas CD40L-overexpressing mice develop high-titer autoantibodies and chronic inflammation.^{5,6} Here, we report the first 2 subjects, a boy (III.1) and his mother (II.2), with *CD40LG* duplication-associated autoimmune diseases (Fig 1, A).

The index subject, III.1, presented as a 6-month-old boy with coombs-positive hemolytic anemia, which evolved into multilineage autoimmune cytopenias associated with massive splenomegaly. Peripheral blood flow cytometric analysis revealed moderate T-cell lymphopenia and mild B-cell lymphopenia with increased frequencies of CD45RO⁺ memory T cells, CD27⁺IgD⁺ class-switched memory B cells, and plasmablasts (see Table E1 and Fig E1 in this article's Online Repository at www.jacionline.org). Although initial immunoglobulin A, G, and M serum concentrations exceeded age-matched control ranges, IgM progressively declined until subject III.1 became selectively IgM deficient at age 5 years (Table E1). His autoimmune cytopenias were refractory to glucocorticoids, rapamycin, intravenous immunoglobulin, and rituximab.

Subject II.2 presented as a 25-year-old woman with Raynaud phenomenon and arthralgia. Serologic testing revealed high-titer antinuclear (1:320), antiribonucleoprotein (>8 Avidity Index [AI]), and antithyroid antibodies. She was diagnosed with mixed connective tissue disease and autoimmune thyroiditis. After 8 years, her symptoms resolved spontaneously during pregnancy. Recent serological testing demonstrated lower antinuclear antibody and ribonucleoprotein titers (1:160 and 0.4 AI, respectively).

To identify a genetic basis for our subjects' autoimmune diseases, we performed whole-exome sequencing. Pathologic mutations, including autoimmune lymphoproliferative syndrome-associated

METHODS

Design and data collection

This study is an analysis of cross-sectional survey data linked to publicly available data on road locations, area social and economic characteristics, and crime. Survey data were collected for the Study of Asthma in Children of Mexican Descent, a population-based, cross-sectional study conducted with participants in a larger study, the Chicago Asthma School Study (CASS).^{E1} From January to April, 2004, parents of 9895 students grades K-8 from 15 public schools in Chicago responded to a 2-page asthma screener as part of CASS.^{E1} A total of 6896 students enrolled in CASS in that period were of Mexican descent and between August 2004 and April 2005 parents of all Mexico-born ($n = 1366$) and a random sample of US-born ($n = 1485$) were invited to complete a mailed questionnaire or a telephone interview about respiratory conditions and factors related to asthma in their children.^{E2} The parents of 2023 children responded; 91% of the parents answered in Spanish. After excluding all participants with missing data on respiratory outcomes and variables of interest, the final analysis was based on data for 1925 children. The current analysis was approved by the Institutional Review Board of the University of Illinois at Chicago.

Proximity to traffic

We geocoded the residential addresses of participants using geographic information system software (ArcMap 10.2, ESRI, Redlands, Calif). The locations of all primary arterials were obtained from the Illinois Department of Transportation for the year 2004.^{E3} IDOT describes primary arterials as roads that are capable of moving large volumes of traffic at relatively high speeds over long distances.^{E3} For this analysis, proximity to traffic was categorized as 0 to 150 m, 151 to 250 m, 251 to 500 m, and more than 500 m distance from primary traffic arterials, similar to the scheme used in previous investigations.^{E4-E9} Because the associations of proximity to traffic with the outcome variables were similar for the lowest 2 categories (0-150 m and 151-250 m) and the highest 2 categories (251-500 m and >500 m), we later defined proximity to traffic as a binary variable (within 250 m vs over 250 m). We did not examine shorter distances to primary arterials because only a limited number of participants resided within 50 m ($n = 17$) or 100 m ($n = 52$).

Respiratory outcomes

Lifetime asthma was defined on the basis of parent's response to the question "Has a doctor ever said that your child had asthma?"^{E10} The questionnaire also included standardized questions^{E11} on parent report of lifetime wheezing (child ever had wheezing or whistling in the chest any time in the past) and current wheezing (wheezing or whistling in the chest in the last 12 months).

Individual- and neighborhood-level covariates

Individual-level characteristics that were treated as potential confounders in the analysis included age (4-7, 8-11, and 12-18 years), having access to a regular doctor or clinic, ear infection in first year of life, viral infection in first year of life, antibiotics use in first year of life, breast-feeding, number of children in the home (≥ 2 , 1, or 0), day-care or preschool attendance, maternal smoking during pregnancy, current smoking in the home, *in utero* exposure to cats or dogs as well as birds, and current exposure to cats or dogs as well as birds. In addition, we examined the potential confounding and moderating effects of sex, parental history of asthma or allergies, child's history of any allergies to foods or medications, country of birth (United States, except Puerto Rico vs Mexico), length of residence in the United States (for Mexico-born children), having a smoker present at home at the time of child's birth, neighborhood deprivation, and neighborhood crime.

Neighborhood deprivation was estimated using a composite index with 6 indicators of socioeconomic status for a given census tract (year 2000 US Census data): percent of adults 25 years or older with less than a high school degree; percent of unemployed males; percent of households receiving public assistance; percent of households with income below the federal poverty line;

percent of female-headed households with children; and median household income.^{E12} Data on the number of crimes for the year 2004 for a given census tract were aggregated from the Chicago Police Department data portal (<https://data.cityofchicago.org>). Census tract population density was calculated as the number of people residing within a census tract (based on year 2000 US Census estimates) divided by the area of the census tract (calculated in square miles).

Statistical analyses

We compared the proportions of children with the outcome variables across the 4-level traffic exposure variable as well as covariates using chi-square statistics. Multilevel logistic regression analyses using generalized estimating equations were performed to estimate the OR for each of the exposure categories (0-150 m, 151-250 m, and 251-500 m) compared with residence more than 500 m from primary traffic arterials as the reference category. To account for potential neighborhood clustering of children enrolled in the study, we specified child's neighborhood as the cluster effect. A change of 10% or more in the respiratory outcome-traffic-related exposure association of interest with the addition of a specific covariate was considered evidence of confounding.^{E13,E14} All neighborhood-level variables were standardized (mean, 0; SD, 1) before they were considered in logistic regression models. In separate adjusted models, we also examined the interactions between the binary traffic-related exposure variable (≤ 250 m vs > 250 m) and potential moderators by adding the product term to the logistic regression models. A P value of .05 or less was used to indicate statistical significance for all analyses. All analyses were conducted using SAS version 9.4 (Cary, NC).

REFERENCES

- E1. Eldeirawi KM, Persky VW. Associations of physician-diagnosed asthma with country of residence in the first year of life and other immigration-related factors: Chicago asthma school study. *Ann Allergy Asthma Immunol* 2007;99:236-43.
- E2. Eldeirawi K, McConnell R, Furner S, Freels S, Stayner L, Hernandez E, et al. Associations of doctor-diagnosed asthma with immigration status, age at immigration, and length of residence in the United States in a sample of Mexican American School Children in Chicago. *J Asthma* 2009;46:796-802.
- E3. Illinois Highway Information System: Roadway Information and Procedure Manual. Springfield (IL): Illinois Department of Transportation (IDOT); 2001.
- E4. McConnell R, Berhane K, Yao L, Jerrett M, Lurmann F, Gilliland F, et al. Traffic, susceptibility, and childhood asthma. *Environ Health Perspect* 2006;114:766-72.
- E5. Ryan PH, LeMasters G, Biagini J, Bernstein D, Grinshpun SA, Shukla R, et al. Is it traffic type, volume, or distance? Wheezing in infants living near truck and bus traffic. *J Allergy Clin Immunol* 2005;116:279-84.
- E6. Cesaroni G, Badaloni C, Romano V, Donato E, Perucci CA, Forastiere F. Socio-economic position and health status of people who live near busy roads: the Rome Longitudinal Study (RoLS). *Environ Health* 2010;9:41.
- E7. Chang J, Delfino RJ, Gillen D, Tjoa T, Nickerson B, Cooper D. Repeated respiratory hospital encounters among children with asthma and residential proximity to traffic. *Occup Environ Med* 2009;66:90-8.
- E8. Cook AG, Devos AJBM, Pereira G, Jardine A, Weinstein P. Use of a total traffic count metric to investigate the impact of roadways on asthma severity: a case-control study. *Environ Health* 2011;10:52.
- E9. Zhou Y, Levy JI. Factors influencing the spatial extent of mobile source air pollution impacts: a meta-analysis. *BMC Public Health* 2007;7:89.
- E10. Centers for Disease Control and Prevention (CDC). National Health and Nutrition Examination Survey Questionnaire. Hyattsville, Md: National Center for Health Statistics (NCHS); 2001-2002.
- E11. International Study of Asthma and Allergy in Children (ISAAC). Phase Three Manual. Auckland, New Zealand: ISAAC International Data Centre; 2000.
- E12. Bird CE, Seeman T, Escarce JJ, Basurto-Davila R, Finch BK, Dubowitz T, et al. Neighbourhood socioeconomic status and biological 'wear and tear' in a nationally representative sample of US adults. *J Epidemiol Community Health* 2010;64:860-5.
- E13. Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health* 1989;79:340-9.
- E14. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol* 1993;138:923-36.