Peptic ulcer as mediator of the association between risk of gastric cancer and socioeconomic status, tobacco smoking, alcohol drinking, and salt intake

Giulia Collatuzzo[1], Gianfranco Alicandro[2,3], Paola Bertuccio[4,5], Claudio Pelucchi[4], Rossella Bonzi[4], Domenico Palli[6], Monica Ferraroni[4], Weimin Ye[7], Amelie Plymoth[7], David Zaridze[8], Dmitry Maximovich[8], Nuria Aragones[9,10], Gemma Castaño-Vinyals[9,11,12,13] (authorship for study SPAIN 1 to be confirmed by the PIs), Jesus Vioque[9,14], Manoli Garcia de la Hera[9,14], Zuo-Feng Zhang[15], Jinfu Hu[16], Lizbeth López-Carrillo[17], Malaquias López-Cervantes[18], Michela Dalmartello[4], Lina Mu[19], Mary H. Ward[20], Charles S. Rabkin[20], Guo-Pei Yu[21], M. Constanza Camargo[20], Maria Paula Curado[22], Nuno Lunet[23,24,25], Eva Negri[1,4], Carlo La Vecchia[4], Paolo Boffetta[1,26]

1 Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
2 Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy
3 Cystic Fibrosis Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy
4 Department of Clinical Sciences and Community Health, Branch of Medical Statistics, Biometry and Epidemiology "G.A. Maccacaro", Università degli Studi di Milano, Milan, Italy
5 Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Pavia, Italy
6 Cancer Risk Factors and Life-Style Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network, ISPRO, Florence, Italy
7 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
8 Department of Epidemiology and Prevention, Russian N.N. Blokhin Cancer Research Center, Moscow, Russia
9 Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Madrid, Spain
10 Cancer Epidemiology Section, Public Health Division, Department of Health of Madrid, Spain
11 Barcelona Institute for Global Health—ISGlobal, Barcelona, Spain
12 IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain
13 Universitat Pompeu Fabra (UPF), Barcelona, Spain
14 Instituto de Investigación Sanitaria y Biomédica de Alicante, Universidad Miguel Hernandez (ISABIAL-UMH), Alicante, Spain
15 Department of Epidemiology, UCLA Fielding School of Public Health and Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA
16 Harbin Medical University, Harbin, China
17 Mexico National Institute of Public Health, Morelos, Mexico
18 Facultad de Medicina, UNAM. Coyoacán, 04510, Mexico
19 Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, Buffalo, NY, USA

20 Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD, United States
21 Medical Informatics Center, Peking University, Peking, China
22 Centro Internacional de Pesquisa, A. C. Camargo Cancer Center, São Paulo, Brasil
23 EPIUnit – Instituto de Saúde Pública da Universidade do Porto, Porto, Portugal
24 Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional (ITR), Porto, Portugal
25 Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina da Universidade do Porto, Porto, Portugal
26 Stony Brook Cancer Center, Stony Brook University, Stony Brook, NY, USA

Corresponding author
Paolo Boffetta, MD, MPH
Stony Brook Cancer Center
Stony Brook University
Lauterber Dr
Stony Brook, NY, 11794 USA
Email paolo.boffetta@stonybrookmedicine.edu

Word count
Abstract: 207
Text: 2851

Abstract

Peptic ulcer disease (PUD) and gastric cancer (GC) are more prevalent in low socioeconomic status (SES) individuals and share several risk factors. The aim of this study was to investigate the mediating role of PUD in the association between established risk factors and GC. To this aim, we conducted a pooled analysis of 12 studies from the Stomach cancer Pooling (StoP) Project Consortium, including a total of 4,877 GC cases and 11,808 controls. We explored the mediating role of PUD in the association between SES, tobacco smoking, heavy alcohol drinking and salt intake, and GC. Also, we assessed the ORs and 95% CIs of the risk factors and both PUD and GC. Our results showed PUD mediates 36% of the smoking effect mainly among men. Other risk factors were only slightly mediated by PUD (SES 5.3%, heavy alcohol drinking 3.3%, salt intake 2.5%). No significant difference was found when excluding PUD diagnosed within 2 years from GC. Our study provides innovative information on the mechanism of stomach mucosal damage leading to PUD and GC, in particular with respect to the effect of tobacco smoking.

Introduction

Despite its declining incidence and mortality (1), gastric cancer (GC) remains one of the most common neoplasms, representing the fifth most common cancer and the fourth cause of cancer mortality worldwide (2). Its burden concerns especially low socioeconomic status (SES) groups of the population.

Besides the key role of Helicobacter pylori (Hp), lifestyle factors such as smoking, alcohol drinking, low fiber consumption and high red meat and salt intake play an important role in GC occurrence (3,4). Indeed, lifestyle habits have been hypothesized to partly explain the link between GC and low SES. Recently, we described a mediation role of a score combining different lifestyle factors (tobacco smoking, heavy alcohol drinking, low intake of fruit, vegetables, and processed meat and salt), which explained 10% of the effect of low SES among men in studies participating in the Stomach cancer Pooling (StoP) Project Consortium (5). Around 10% of people worldwide develop peptic ulcer disease (PUD) lifelong (6). The discovery of Hp as the main etiological factor of PUD, led to a preventive strategy through eradication of the bacterium with common antibiotics (6) (7). Anyway, PUD remains a severe disease, with a minority of patients necessitating surgery (8).
Nowadays, the challenges are represented by the etiological classification of the disease (9), and the differential diagnosis between neoplastic and preneoplastic conditions. In fact, it is unclear whether the strong association between PUD and GC can be explained by PUD being an ulcerative lesion of the neoplasm, or by the fact that PUD is a separate lesion associated with higher risk of developing GC (10). PUD has strong socioeconomic disparity (11), with higher rates of complications and mortality among disadvantaged subgroups of the population and in less developed countries (12).

The StoP Consortium provides a unique opportunity to address this complex relationship in a large population of GC cases and controls. In particular, we aimed at exploring the mediation role of PUD in the relationship between SES, tobacco smoking, alcohol drinking and salt intake and the risk of GC.

Methods

We used data from the StoP-Project, an international consortium of 34 studies on GC, including individual-data from 13,121 GC cases and 31,420 controls (version 3.2 of the StoP database) (13).

To participate in the consortium, principal investigators of the studies signed a data transfer agreement and provided a copy of the original dataset to the coordinating center. All data were harmonized according to a standard format at the data center (13). The StoP-Project received ethical approval from the University of Milan Institutional Review Board.

For the present analysis, we pooled data from 12 studies with information on PUD, SES, and tobacco smoking (14-25). Details about the studies are in Supplementary Table 1. In addition to excluding studies that did not collected information of one or more of these factors, we excluded those with more than 10% missing values for PUD or SES, as well as 4 studies with reported prevalence of PUD in controls higher than 20% or lower than 1%. Information on alcohol drinking was not available in one of the 12 studies, and that on salt intake in two. In five of the studies information on date of PUD was also available: they were included in a secondary analysis from which subjects with PUD diagnosed within 2 years from date of GC diagnosis or interview were excluded, to address potential reverse causality between PUD and GC.

We considered SES, tobacco smoking, alcohol drinking and salt intake as exposures. To measure SES, we used a variable comprising education, occupation and income, based on study-specific indicators. In preliminary analyses, we also considered the highest attained level of education as proxy of SES; since the results were very close to those based on SES, we do not report them in detail. We generated dichotomous variables for each exposure: low vs medium-high level of SES, based on study-specific categories, never vs ever tobacco smoking, no-moderate alcohol vs heavy alcohol drinking (i.e., 47 or more g ethanol/day), and low-medium vs high consumption of salt, based on study specific tertiles.

The mediator of our analysis was self-reported history of PUD. In some studies, separate information was collected on gastric and duodenal ulcer; however, in the present analyses, PUD accounted for history of either gastric or duodenal ulcer.

First, we estimated the pooled odds ratios (OR) of GC and their corresponding 95% confidence intervals (CI) through multivariable logistic regression models, for each exposure, including SES, smoking status, alcohol drinking, salt intake and history of PUD, as binary exposures. OR among categories of socioeconomic status and tobacco smoking was obtained from a core model including sex, age (<50, 50-60, 61-65, 66-69, 70-74, 75+), study, socioeconomic status and tobacco smoking as explanatory variables. PUD was added to the core model to obtain the OR among subjects with PUD. Alcohol drinking and salt intake was alternatively added

to the core model to obtain the corresponding OR. Second, we used the same analytic approach to investigate the association between the same risk factors and PUD, both among controls only and within the whole study population, adjusting for GC case/control status.

For the mediation analysis, we used the dichotomous variables for PUD and the risk factors described above, and decomposed the total effect of each factor into a natural direct effect and a natural indirect effect, the latter being the effect explained by the mediation effect of PUD, and calculated the proportion of mediation (PM) as the ratio between the log of the natural indirect effect and that of the total effect (26,27). The mediation analysis was performed by using the command *paramed* in STATA (StataCorp etc.) (28).

The following additional analyses were performed to explore the mediating role of PUD: (i) excluding cases and controls with PUD diagnosed within 2 years from GC diagnosis or interview; (ii) stratifying by sex; (iii) considering a subset of nine studies with data available for all risk factors, to increase comparability of results across risk factors.

Results

Table 1 shows the distribution of the main characteristics of the study population. The pooled dataset comprised 16,685 subjects, including 4,877 cases and 11,808 controls. Median age was 64 (IQR 56-71) among cases and 62 (IQR 52-70) among controls. Compared to controls, cases were more often heavy current smokers, heavy alcohol drinkers, with lower SES, and they more often reported history of PUD, while there was only a small difference in salt intake between cases and controls. The overall prevalence of history of PUD (either gastric or duodenal) was 12.0% (19.0% among cases, 9.1% among controls).

Table 2 illustrates the association between each risk factor and GC (i.e. the outcome) and PUD (i.e. the mediator) separately. GC was positively associated PUD, heavy smoking, increasing alcohol consumption, low SES, and increasing salt intake. The OR of GC for history of PUD was 2.36 (95% CI 2.13-2.62). When excluding ulcers diagnosed within 2 years from GC diagnosis (Supplementary table 2), the corresponding OR was 2.12 (95% CI 1.76-2.55).

In the analysis restricted to controls, there was an association between history of PUD and female sex (OR=0.62, 0.53-0.72), older age (p for trend <0.001), SES (0.78, 0.68-0.90) and tobacco smoking (1.78, 1.53-2.08, p<0.001). Those associations were confirmed also in the analysis with cases and controls, after adjusting for case/control status (Supplementary Table 2).

Table 3 illustrates the results of the mediation analysis on the whole study population. The primary analysis revealed that PUD mediated 36.2% of the risk exerted by tobacco smoking. On the other hand, PUD mediated only a small amount of the risk of GC from SES (5.3%), heavy alcohol drinking (3.3%) and salt intake (2.5%).
When the analysis was repeated in the subset of studies with complete information (Table 4), results were confirmed (PMs were: 44.3% for tobacco smoking, 7.7% for SES, 2.0% for heavy alcohol drinking, and 0.8% for salt intake).

Results of the mediation analysis on tobacco smoking stratified by sex are illustrated in Figure 1: among men, the OR of natural direct effect was 1.14, that of natural indirect effect was 1.06 (PM=31.6%), among women, the ORs were 1.00 and 1.03, respectively (PM=88.3%).

The results of the sensitivity analysis excluding subjects whose PUD was diagnosed less than two years before GC or interview, showed substantially comparable results with those of the main analysis (Supplementary Table 3).

Discussion

We presented the results of a pooled analysis of 12 studies investigating the mediation role of PUD in the association between several risk factors and GC. This approach provides an original contribution to an understanding of the relationship between PUD and GC, and how established risk factors of GC may exert their effect.

Besides confirming the association with known risk factors, our results indicate that PUD mediates about 36% of the effect of tobacco smoking, while the mediation effect was smaller for the other risk factors. The results were robust to the exclusion of recently diagnosed PUD, arguing against reverse causality in the relationship between PUD and GC.

Our results are in agreement with those of previous studies, that have identified low SES, tobacco smoking, high alcohol drinking and high salt intake as risk factors of GC (3,4,29). Also, we identified a strong association between PUD and GC (10,30). In particular, the risk of GC among subjects with history of PUD remained elevated when considering only PUD diagnosed more than two years before GC diagnosis of interview, despite the fact that several studies indicated that the highest risk of GC occurs in the first 2 years from PUD diagnosis (10,31,32).

Components of SES, including education, occupation and income may be markers of other risk factors of disease (33). Mediation analysis complements statistical adjustment by describing the proportion of risk of disease exerted by a given factor, which is attributable to another factor (the mediator) (26,27).

Both GC and PUD are observed more commonly in the lowest SES strata of the population, representing an important cause of disease disparity (34,35). Education, a major component of SES, is related to conditions and lifestyle factors predisposing to disease (36-39): habits as smoking and alcohol drinking are clustered in less affluent groups, as well as low-quality diet, including highly salted diet (40); low education also correlates with exposure to occupational carcinogens, and with poor hygienic conditions (33). Indeed, higher prevalence of Hp infection, which is the main cause of both PUD and GC, can be observed in middle and low income countries, particularly among subjects living in crowded places, and with no access to potable water (33,41,42).

Based on our analysis, the association between SES and GC is mediated by PUD only to a limited extent. In a previous study, we explored the mediation role of lifestyle factors in the association

between education and GC, without individuating an element justifying this strong and significant relationship (5).

Conversely, PUD mediates the association between tobacco smoking and GC. In particular, about one third of this excess risk of GC due to tobacco smoking appears to be mediated by PUD. This is consistent with the fact that tobacco smoking is strongly linked to PUD. Tobacco smoking may damage gastric mucosa, leading to PUD, by multiple mechanisms, including (i) inhibition of mucus synthesis (ii) inhibition of angiogenesis through the dysregulation of nitric oxide (NO) production (iii) mucosal ischemia due to microvascular alteration (iv) cellular lesions due to increased reactive oxygen species and mechanical effects (43). Long-term smoking increases acid secretion, leading to a lower stomach pH; it also modifies mucus production, reduces mucosal repair, alters microcirculation and significantly reduces blood flow to the gastrointestinal mucosa, which may favor the development of inflammatory diseases. Moreover, nicotine compromise gastric mucosal blood flow, causing also delayed healing and increased relapse of the disease (44).

Elevated alcohol intake was associated to GC in this analysis, as well as in previous analyses based on the StoP Consortium (45), but the association with PUD was not significant. This agrees with a large study from Denmark, that found no relation between alcohol drinking and PUD (46), as well as with a previous review, in which the majority of studies did not associate heavy alcohol drinking with duodenal ulcer (47). As a consequence, PUD did not appear to be an important mediator of the relationship between alcohol drinking and GC risk.

Similarly, elevated salt intake was associated with risk of GC but the association with PUD was weak and non-significant. As a consequence, PUD had no relevant mediating role in the association between high salt intake and GC risk. Several studies reported higher mortality from gastric ulcer (48), but no material relationship with duodenal ulcer in subjects with highly salted diet (49). Salty diet is a probable risk factor of GC (50). Anyway, little is known on the mechanisms beyond this association. An inverse relation between sodium concentrations and Hp growth and virulence factors has been described (51). However, salt may damage gastric mucosa by potentiating Hp carcinogenicity (52), though the increase of CagA protein transcription, associated with higher risk of PUD and GC (53,54); also, salt alters gastric osmolarity and time of stomach emptying, prolonging the contact of stomach mucosa with potential harmful substances (52). A study based on Mongolian gerbil model has shown higher risk of gastric ulceration in Hp infected animals assigned

to a highly-salted diet program, with salt being related to mucous microenvironment impairment predisposing to Hp damage (55). Cag-A up-regulation was confirmed in bacterial culture (56).

The results of the stratified analysis by sex suggest a higher role of PUD in the association between tobacco smoking and GC among women compared to men, although the overall effect was stronger in the latter. This is likely explained by the large number of men who smoked (71.7% of controls) compared to women (27.9%) in this population.

Our results imply that identification and treatment of PUD among smokers may be of particular importance as a tool to reduce GC risk. Conversely, this does not appear to be the case for two other behavior-related risk factors of GC, i.e., heavy alcohol and salt intake. The sensitivity analysis performed excluding PUD diagnosed in the 2 years before GC diagnosis supports the main findings, confirming that PUD a separate entity which anticipates the development of stomach malignancy rather than a marker of incipient GC.

Data collection was based on self-reported information on exposure to risk factors, including PUD, which may partially affect the analysis through recall bias. The direction and magnitude of this bias depends on the degree of misclassification of information on PUD and other risk factors, and whether this was differential between GC cases and controls, making its effect difficult to predict. Moreover, the included studies are of retrospective case-control design, therefore prone to selection bias. This is especially relevant for hospital-based studies (14,16,19,23,24). However, the findings are not heterogeneous between hospital and population-based controls. Furthermore, we did not have accurate information on Hp status for a large part of the subjects included in the analysis, which prevented us from adjusting the analysis for this important risk factor of both PUD and GC. Although Hp infection does not appear to be associated with tobacco smoking (57), its persistence may be (58), suggesting that some residual confounding on the role of PUD as mediator of the carcinogenic effect of tobacco smoking cannot be excluded. Next, we pooled data of studies conducted in a large timeframe (1985-2012), entailing some heterogeneity in diagnostic criteria for both PUD and GC. This issue was addressed by adjusting for the single included studies in the different models. Finally, we were not able to distinguish gastric and duodenal ulcers. Despite this, our aim was to study PUD overall, and we were able to account for both types of ulcers.

The present study has several strengths. The pooled analysis allowed the investigation on a large set of cases of GC. Also, we put together detailed sociodemographic, clinical and lifestyle-related data,

enabling to perform accurate analyses. We followed a well assessed method for mediation analysis, and we performed sensitivity analyses to assess the robustness of our results. Additionally, we assessed the robustness of our results by conducting several sensitivity analyses, which overall highlighted the overall validity of our investigation.
In conclusion, we offer original and new insight to a stomach disease epidemiology, which describes how established risk factors act in promoting GC.

This study contributes to clarifying the mechanisms underlying gastric carcinogenesis from an epidemiologic perspective. PUD appears to mediate about one third of the excess risk exerted by tobacco smoking on GC, representing a clinical flag for surveillance among smokers. Conversely, other known risk factors of GC do not appear to be mediated by PUD.

Authors' contributions: Conception and design of study: GC, GA, PBe, EN, PBo; acquisition of data: DP, MF, WY, AP, DZ, DM, NA, GCV, JV, MGH, ZFZ, JH, LLC, MLC, MD, LM, MHW, CSR, GPY, MCC, MPC, NL, EN, CLV; management, analysis and interpretation of data: GC, GA, PBe, CP, RB, PBo; drafting the manuscript: GC, PBo; revising the manuscript critically for important intellectual content: GA, PBe, CP, EN, CLV; approval of final manuscript: all authors.

Conflict of interest: The authors have no conflicts to report.

Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request and approval by members of StoP-project Consortium.

Ethics Statement: The StoP Project has been approved by the Institutional Review Board of the University of Milan. The parent studies have been approved by relevant Institutional Review Boards.

Funding: This study was funded by the Associazione Italiana per la Ricerca sul Cancro (AIRC), Project no. 21378 (Investigator Grant). The authors thank the European Cancer Prevention (ECP) Organization for providing support for the project meetings.

Acknowledgement: NA

References

1- Zhang T, Chen H, Zhang Y, et al. Global changing trends in incidence and mortality of gastric cancer by age and sex, 1990-2019: Findings from Global Burden of Disease Study. J Cancer. 2021;12:6695-705.

2- Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71:209-49.

3- Cavatorta O, Scida S, Miraglia C, et al. Epidemiology of gastric cancer and risk factors. Acta Biomed. 2018;89:82-7.

4- Lyons K, Le LC, Pham YT, et al. Gastric cancer: epidemiology, biology, and prevention: a mini review. Eur J Cancer Prev. 2019;28:397-412.

5- Alicandro G, Bertuccio P, Collatuzzo G, et al. The mediating role of combined lifestyle factors on the relationship between education and gastric cancer in the Stomach cancer Pooling (StoP) Project. Submitted for publication.

6- Lanas A, Chan FKL. Peptic ulcer disease. Lancet. 2017;390:613-24.

7- Talamini G, Tommasi M, Amadei V, et al. Risk factors of peptic ulcer in 4943 inpatients. J Clin Gastroenterol. 2008;42:373-80.

8- Howley IW, Bruns BR, Tesoriero RB, et al. Statewide Analysis of Peptic Ulcer Disease: As Hospitalizations Decrease, Procedural Volume Remains Steady. Am Surg. 2019;85:1028-32.

9- Quan C, Talley NJ. Management of peptic ulcer disease not related to Helicobacter pylori or NSAIDs. Am J Gastroenterol. 2002;97:2950-61.

10- Lee TY, Wang CB, Chen TT, et al. A tool to predict risk for gastric cancer in patients with peptic ulcer disease on the basis of a nationwide cohort. Clin Gastroenterol Hepatol. 2015;13:287-93.

11- Havens JM, Castillo-Angeles M, Nitzschke SL, Salim A. Disparities in peptic ulcer disease: A nationwide study. Am J Surg. 2018;216:1127-8.

12- Stewart B, Khanduri P, McCord C, Ohene-Yeboah M, Uranues S, Vega Rivera F, Mock C. Global disease burden of conditions requiring emergency surgery. Br J Surg. 2014;101:e9-22.

13- Pelucchi C, Lunet N, Boccia S, et al. The stomach cancer pooling (StoP) project: study design and presentation. Eur J Cancer Prev. 2015;24:16-23.

14- La Vecchia C, D'Avanzo B, Airoldi L, Braga C, Decarli A. Nitrosamine intake and gastric cancer risk. Eur J Cancer Prev. 1995;4:469-74.

15- Deandrea S, Foschi R, Galeone C, La Vecchia C, Negri E, Hu J. Is temperature an effect modifier of the association between green tea intake and gastric cancer risk? Eur J Cancer Prev. 2010;19:18-22.

16- Lucenteforte E, Scita V, Bosetti C, Bertuccio P, Negri E, La Vecchia C. Food groups and alcoholic beverages and the risk of stomach cancer: a case-control study in Italy. Nutr Cancer. 2008;60:577-84.

17- Buiatti E, Palli D, Decarli A, et al. A case-control study of gastric cancer and diet in Italy. Int J Cancer. 1989;44:611-6.
18- Mu LN, Lu QY, Yu SZ, et al. Green tea drinking and multigenetic index on the risk of stomach cancer in a Chinese population. Int J Cancer. 2005;116:972-83.
19- Zaridze D, Borisova E, Maximovitch D, Chkhikvadze V. Aspirin protects against gastric cancer: results of a case-control study from Moscow, Russia. Int J Cancer. 1999;82:473-6.
20- Setiawan VW, Zhang ZF, Yu GP, et al. Protective effect of green tea on the risks of chronic gastritis and stomach cancer. Int J Cancer. 2001;92:600-4.
21- Castaño-Vinyals G, Aragonés N, Pérez-Gómez B, et al. Population-based multicase-control study in common tumors in Spain (MCC-Spain): rationale and study design. Gac Sanit. 2015;29:308-15. Erratum in: Gac Sanit. 2018;32:501.
22- Ye W, Ekström AM, Hansson LE, Bergström R, Nyrén O. Tobacco, alcohol and the risk of gastric cancer by sub-site and histologic type. Int J Cancer. 1999;83:223-9.
23- Santibañez M, Alguacil J, de la Hera MG, Navarrete-Muñoz EM, et al. Occupational exposures and risk of stomach cancer by histological type. Occup Environ Med. 2012;69:268-75.
24- López-Carrillo L, López-Cervantes M, Robles-Díaz G, et al. Capsaicin consumption, Helicobacter pylori positivity and gastric cancer in Mexico. Int J Cancer. 2003;106:277-82.
25- Ward MH, Sinha R, Heineman EF, et al. Risk of adenocarcinoma of the stomach and esophagus with meat cooking method and doneness preference. Int J Cancer. 1997;71:14-9.
26- Vanderweele TJ, Vansteelandt S. Conceptual issues concerning mediation, interventions and composition. Stat Interface. 2009;2:457–468.
27- Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychol Methods. 2013;18:137-50. Erratum in: Psychol Methods. 2013;18:474.
28- Emsley R, Liu H. PARAMED: Stata module to perform causal mediation analysis using parametric regression models. Statistical software components. Boston: Boston College Department of Economics; 2013.
29- De Martel C, Parsonnet J. Stomach Cancer. In Thun M, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D. Cancer Epidemiology and Prevention. New York, NY: Oxford University Press, 2018.
30- Hwang JJ, Lee DH, Lee AR, et al. Characteristics of gastric cancer in peptic ulcer patients with Helicobacter pylori infection. World J Gastroenterol. 2015;21:4954-60.
31- Hansson LE, Nyrén O, Hsing AW, et al. The risk of stomach cancer in patients with gastric or duodenal ulcer disease. N Engl J Med. 1996;335:242-9.
32- Molloy RM, Sonnenberg A. Relation between gastric cancer and previous peptic ulcer disease. Gut. 1997;40:247-52.

33- Kogevinas M, Pearce N, Susser M, Boffetta P, Eds. Social Inequalities and Cancer. IARC Scientific Publication No. 138. Lyon, France: IARC, 1997.
34- Alicandro G, Frova L, Sebastiani G, El Sayed I, Boffetta P, La Vecchia C. Educational inequality in cancer mortality: a record linkage study of over 35 million Italians. Cancer Causes Control. 2017;28:997-1006.
35- Lagergren J, Andersson G, Talback M, et al. Marital status, education, and income in relation to the risk of esophageal and gastric cancer by histological type and site. Cancer. 2016;122:207-12.
36- Sarkar S, Dauer MJ, In H. Socioeconomic Disparities in Gastric Cancer and Identification of a Single SES Variable for Predicting Risk. J Gastrointest Cancer. 2021;10.1007/s12029-020-00564-z.
37- Yegen BC. Lifestyle and Peptic Ulcer Disease. Curr Pharm Des. 2018;24:2034-40.
38- Havens JM, Castillo-Angeles M, Nitzschke SL, Salim A. Disparities in peptic ulcer disease: A nationwide study. Am J Surg. 2018;216:1127-8.
39- Rota M, Alicandro G, Pelucchi C, et al. Education and gastric cancer risk-An individual participant data meta-analysis in the StoP project consortium. Int J Cancer. 2020;146:671-81.
40- Schuit AJ, van Loon AJ, Tijhuis M, Ocké M. Clustering of lifestyle risk factors in a general adult population. Prev Med. 2002;35:219-24.
41- Malaty HM, Graham DY. Importance of childhood socioeconomic status on the current prevalence of Helicobacter pylori infection. Gut. 1994;35:742-5.
42- Laszewicz W, Iwańczak F, Iwańczak B; Task Force of the Polish Society of Gastroenterology; Task Force of the Polish Society of Gastroenterology. Seroprevalence of Helicobacter pylori infection in Polish children and adults depending on socioeconomic status and living conditions. Adv Med Sci. 2014;59:147-50.
43- Berkowitz L, Schultz BM, Salazar GA, et al. Impact of Cigarette Smoking on the Gastrointestinal Tract Inflammation: Opposing Effects in Crohn's Disease and Ulcerative Colitis. Front Immunol. 2018;9:74.
44- Maity P, Biswas K, Roy S, Banerjee RK, Bandyopadhyay U. Smoking and the pathogenesis of gastroduodenal ulcer - recent mechanistic update. Mol Cell Biochemistry 2003;253:329-38.
45- Rota M, Pelucchi C, Bertuccio P, et al. Alcohol consumption and gastric cancer risk-A pooled analysis within the StoP project consortium. Int J Cancer. 2017 Nov 15;141(10):1950-1962.
46- Rosenstock S, Jørgensen T, Bonnevie O, Andersen L. Risk factors for peptic ulcer disease: a population based prospective cohort study comprising 2416 Danish adults. Gut. 2003;52:186-93.
47- Franke A, Teyssen S, Singer MV. Alcohol-related diseases of the esophagus and stomach. Dig Dis. 2005;23:204-13.
48- Sonnenberg A. Dietary salt and gastric ulcer. Gut. 1986;27:1138-42. Erratum in: Gut 1986;27:1523.
49- Stemmermann G, Haenszel W, Locke F. Epidemiologic pathology of gastric ulcer and gastric carcinoma among Japanese in Hawaii. J Natl Cancer Inst. 1977;58:13-20.
50- https://www.wcrf.org/wp-content/uploads/2021/01/CUP-Strong-Evidence-Matrix.pdf

51- Gancz H, Jones KR, Merrell DS. Sodium chloride affects Helicobacter pylori growth and gene expression. J Bacteriol. 2008;190:4100-5.
52- Niv Y, Banić M. Gastric barrier function and toxic damage. Dig Dis. 2014;32:235-42.
53- Palli D, Menegatti M, Masala G, et al. Helicobacter pylori infection, anti-cagA antibodies and peptic ulcer: a case-control study in Italy. Aliment Pharmacol Ther. 2002;16:1015-20.
54- Nomura AM, Pérez-Pérez GI, Lee J, Stemmermann G, Blaser MJ. Relation between Helicobacter pylori cagA status and risk of peptic ulcer disease. Am J Epidemiol. 2002;155:1054-9.
55- Kato S, Tsukamoto T, Mizoshita T, et al. High salt diets dose-dependently promote gastric chemical carcinogenesis in Helicobacter pylori-infected Mongolian gerbils associated with a shift in mucin production from glandular to surface mucous cells. Int J Cancer. 2006;119:1558-66.
56- Loh JT, Torres VJ, Cover TL. Regulation of Helicobacter pylori cagA expression in response to salt. Cancer Res. 2007;67:4709-15.
57- Brown LM. Helicobacter pylori: epidemiology and routes of transmission. Epidemiol Rev 2000;22:283–97.
58- Yu J, Yang P, Qin X, Li C, Lv Y, Wang X. Impact of smoking on the eradication of Helicobacter pylori. Helicobacter. 2021:e12860.

Table 1: Characteristics of the study population by selected covariates.

	All subjects (n=16,685)	
Characteristics	**Controls**	**Cases**
Sex		
Male	6,923 (58.6)	3,098 (63.5)
Female	4,885 (41.4)	1,779 (36.5)
Age		
<50	2,434 (20.6)	634 (13.0)
50-60	2,886 (24.5)	1,211 (24.8)
61-65	1,866 (15.8)	824 (16.9)
66-69	1,446 (12.3)	686 (14.1)
70-74	1,667 (14.1)	869 (17.8)
>=75	1,503 (12.7)	653 (13.4)
History of PUD		
No	10,656 (90.9)	3,902 (81.0)
Yes	1,061 (9.1)	915 (19.0)
History of PUD >2 years before cancer diagnosis/interview		
No	3,858 (93.3)	1,674 (85.8)
Yes	277 (6.7)	278 (14.2)
Socioeconomic status		
High	6,009 (51.3)	2,998 (62.0)
Medium	3,654 (31.2)	1,370 (28.3)
Low	2,060 (17.6)	468 (9.7)
Tobacco smoking		
Never	5,429 (46.5)	2,066 (43.1)
Former	3,161 (27.1)	1,236 (25.8)
Low	1,018 (8.7)	418 (8.7)
Medium	1,237 (10.6)	626 (13.1)
High	820 (7.0)	820 (9.3)
Alcohol		
Never	3,000 (28.2)	1,219 (26.7)
Low	3,415 (32.2)	1,145 (25.4)
Medium	2,918 (27.5)	1,523 (33.1)
High	1,290 (12.1)	685 (15.0)
Salt		
Low	3,016 (33.9)	932 (29.6)
Medium	3,609 (40.6)	1,416 (44.9)
High	2,264 (25.5)	806 (25.6)

Numbers may not sum up with the total of study subjects because of missing data
PUD, peptic ulcer disease

Table 2: Odds ratios and 95% confidence intervals of the association between selected characteristics and gastric cancer and peptic ulcer disease

	Gastric cancer	**Peptic ulcer disease§**
Characteristics	**OR, 95% CI**	**OR, 95% CI**
PUD[a]		
No	1.0 (Ref)	-
Yes	2.36 (2.13-2.62)	
Socioeconomic status[b]		
Low	1.0 (Ref)	1.0 (Ref)
Medium-high	0.67 (0.61-0.72)	0.78 (0.68-0.90)
Tobacco smoking[b]		
Never	1.0 (Ref)	1.0 (Ref)
Ever	1.15 (1.06-1.25)	1.78 (1.53-2.08)
Alcohol drinking[c]		
No	1.0 (Ref)	1.0 (Ref)
Yes	1.24 (1.10-1.40)	1.08 (0.87-1.36)
Salt intake[d]		
Low	1.0 (Ref)	1.0 (Ref)
medium-high	1.29 (1.16-1.43)	1.07 (0.90-1.27)

[a] Odds ratio obtained through a logistic regression model including sex, age, study, socioeconomic status, tobacco smoking and peptic ulcer disease as explanatory variables.
[b] Odds ratio obtained through a logistic regression model including sex, age, study, socioeconomic status and tobacco smoking as explanatory variables.
[c] Odds ratio obtained through a logistic regression model including sex, age, study, socioeconomic status, tobacco smoking and alcohol drinking as explanatory variables
[d] Odds ratio obtained through a logistic regression model including sex, age, study, socioeconomic status, tobacco smoking and salt intake as explanatory variables

OR, odds ratio
CI, confidence interval
PUD, peptic ulcer disease
Ref, reference category
§ analysis restricted to controls

Table 3. Analysis of mediation effect of peptic ulcer disease on the association between selected risk factors and gastric cancer (all studies)

	Socioeconomic status	**Tobacco smoking**	**Heavy alcohol drinking***	**Salt intake***
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
NDE	0.67 (0.62-0.73)	1.09 (1.00-1.19)	1.23 (1.09-1.39)	1.28 (1.16-1.42)
NIE	0.98 (0.96-0.99)	1.05 (1.04-1.06)	1.01 (0.99-1.02)	1.01 (0.99-1.02)
TE	0.66 (0.60-0.72)	1.15 (1.06-1.25)	1.24 (1.09-1.41)	1.29 (1.16-1.43)
PM	5.3%	36.2%	3.3%	2.5%

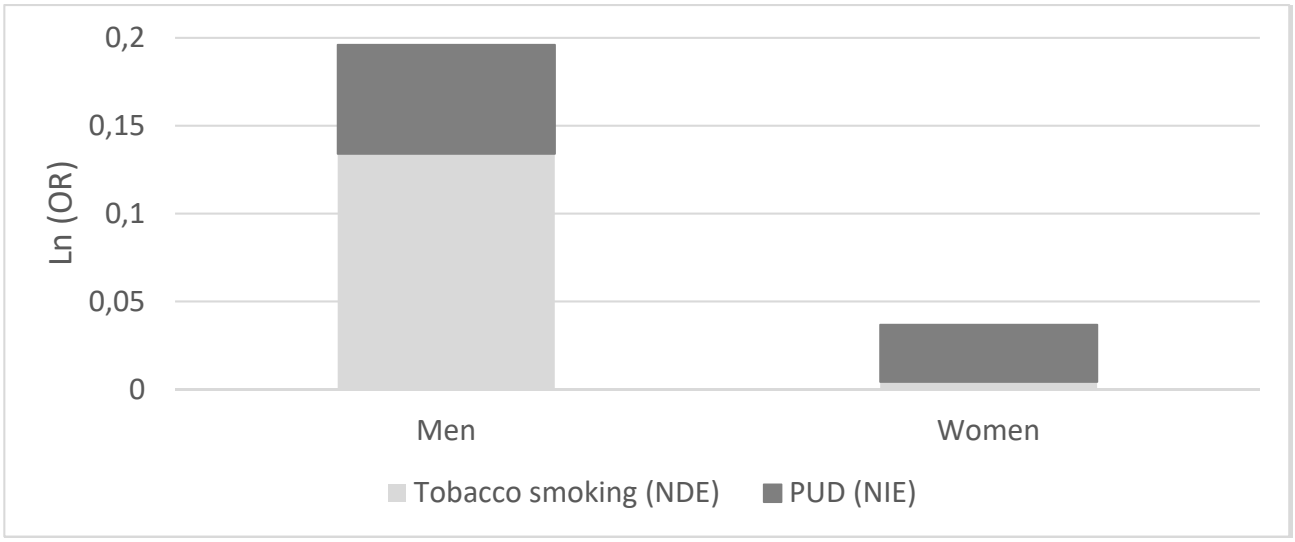
*Analyses were conducted excluding studies with missing information for the exposure
OR, odds ratio
CI, confidence interval
NDE, natural direct effect
NIE, natural indirect effect
TE, total effect
PM, proportion of mediation

Table 4. Analysis of mediation effect of peptic ulcer disease on the association between selected risk factors and gastric cancer (subset of studies with information on all risk factors).

	Socioeconomic status	**Tobacco smoking**	**Heavy alcohol drinking**	**Salt intake**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
NDE	0.73 (0.66-0.80)	1.07 (0.97-1.19)	1.25 (1.10-1.43)	1.26 (1.13-1.40)
NIE	0.97 (0.96-0.99)	1.06 (1.04-1.07)	1.00 (0.99-1.02)	1.00 (0.99-1.01)
TE	0.71 (0.64-0.78)	1.13 (1.03-1.25)	1.26 (1.11-1.43)	1.26 (1.14-1.40)
PM	7.7%	44.3%	2.0%	0.8%

OR, odds ratio
CI, confidence interval
NDE, natural direct effect
NIE, natural indirect effect
TE, total effect
PM, proportion of mediation

Figure 1: Contribution of PUD as a mediator to the association between tobacco smoking in gastric cancer, by sex.



NDE, natural direct effect
NIE, natural indirect effect
PUD, peptic ulcer disease

Supplementary Table 1. Characteristics of the studies included in the pooled analysis.

Study location	Period of enrolment	Design	N cases/controls	Reference
Milan, Italy‡	1985–1997	H	769/2,081	(14)
Harbin, China	1987–1989	P	266/533	(15)
Milan, Italy‡	1997–2007	H	230/547	(16)
Four areas, Italy*	1985–1987	P	1,016/1,159	(17)
Taixing, Jiangsu, China	2000	P	206/415	(18)
Moscow, Russia‡	1996–1997	H	450/611	(19)
Yangzhong, China†	1995	P	133/433	(20)
Ten provinces, Spain	2008–2012	P	441/3,440	(21)
Five counties, Sweden*	1989–1995	P	561/1,164	(22)
Valencia, Spain‡	1995-1999	H	401/455	(23)
3 areas, Mexico	1994-1996	H	234/468	(24)
Nebraska, USA‡	1988-1993	P	170/502	(25)

* Study without information on salt intake.
† Study without information on alcohol drinking.
‡ Study with information on date of ulcer
P, population-based study
H, hospital-based study

Supplementary Table 2: Odds ratios and 95% confidence intervals of the association between selected characteristics and peptic ulcer disease – results of analysis including GC cases and controls

Characteristics	**OR (95% CI)**
Socioeconomic status[a]	
Low	1.0 (Ref)
Medium-high	0.88 (0.78-0.99)
Tobacco smoking[a]	
Never	1.0 (Ref)
Ever	1.79 (1.59-2.01)
Alcohol drinking[b]	
No	1.0 (Ref)
Yes	1.11 (0.94-1.31)
Salt intake[c]	
Low	1.0 (Ref)
medium-high	1.01 (0.88-1.16)

[a] Odds ratio obtained through a logistic regression model including sex, age, study, GC case/control status, socioeconomic status and tobacco smoking as explanatory variables.
[b] Odds ratio obtained through a logistic regression model including sex, age, study, GC case/control status, socioeconomic status, tobacco smoking and alcohol drinking as explanatory variables
[c] Odds ratio obtained through a logistic regression model including sex, age, study, GC case/control status, socioeconomic status, tobacco smoking and salt intake as explanatory variables

OR, odds ratio
CI, confidence interval
Ref, reference category
GC, gastric cancer
* variables added individually to the main model

Supplementary Table 3. Analysis of mediation effect of peptic ulcer disease on the association between selected risk factors and gastric cancer (subset of studies with information on date of ulcer).

	Socioeconomic status	**Tobacco smoking**	**Heavy alcohol drinking**	**Salt intake**
	OR	OR	OR	OR
All PUD				
NDE	0.76 (0.60-0.87)	1.10 (0.96-1.25)	1.14 (0.98-1.31)	1.32 (1.16-1.51)
NIE	0.97 (0.94-1.00)	1.03 (1.01-1.04)	1.00 (0.98-1.02)	1.00 (0.98-1.02)
TE	0.73 (0.63-0.85)	1.13 (0.99-1.29)	1.14 (0.98-1.31)	1.32 (1.16-1.51)
PM	10.2%	22.4%	2.2%	0.0%
PUD diagnosed >2 years before cancer diagnosis/interview				
NDE	0.75 (0.65-0.86)	1.09 (0.95-1.24)	1.12 (0.97-1.29)	1.36 (1.19-1.55)
NIE	0.98 (0.96-1.00)	1.02(1.01-1.04)	1.00 (0.98-1.02)	1.00 (0.88-1.01)
TE	0.73 (0.63-0.85)	1.11 (0.97-1.27)	1.12 (0.97-1.30)	1.35 (1.18-1.55)
PM	6.4%	33.9%	0.0%	0.0%

OR, odds ratio
PUD, peptic ulcer disease
NDE, natural direct effect
NIE, natural indirect effect
TE, total effect
PM, proportion of mediation

----------+

| History of peptic
| ulcer
study | 1 2 | Total
----------+----------+----------
1 | 2,549 299 | 2,848
| 89.50 10.50 | 100.00
----------+----------+----------
3 | 705 72 | 777
| 90.73 9.27 | 100.00
----------+----------+----------
9 | 948 101 | 1,049
| 90.37 9.63 | 100.00
----------+----------+----------
13 | 474 46 | 520
| 91.15 8.85 | 100.00
----------+----------+----------
21 | 3,402 469 | 3,871
| 87.88 12.12 | 100.00
----------+----------+----------
22 | 1,447 274 | 1,721
| 84.08 15.92 | 100.00
----------+----------+----------
23 | 726 127 | 853
| 85.11 14.89 | 100.00
----------+----------+----------
27 | 571 100 | 671
| 85.10 14.90 | 100.00
----------+----------+----------
28 | 227 225 | 452
| 50.22 49.78 | 100.00
----------+----------+----------
29 | 189 90 | 279
| 67.74 32.26 | 100.00
----------+----------+----------
30 | 18 438 | 456
| 3.95 96.05 | 100.00
----------+----------+----------
32 | 547 82 | 629
| 86.96 13.04 | 100.00
----------+----------+----------
36 | 1,102 4 | 1,106
| 99.64 0.36 | 100.00
----------+----------+----------
Total | 12,905 2,327 | 15,232
| 84.72 15.28 | 100.00

MEDIATION ANALYSIS BY ULCER TYPE: GASTRIC (vg2_new) & DUODENAL (vg8_new)

Type of ulcer	SES	SMK	ALCOHOL	SALT
Gastric	4.6%	19.1%	0%	6.7%
Duodenal	0.8%	16.1%	3.7%	0%

NB: the number of studies included, indicated by the variable va2_N, varies a lot and for the last two exposures is markedly reduced when considering each type of ulcer

```
. paramed va1, avar(ses_dico) mvar(vg2_new) cvars(va2_2 va2_5 va2_8 va2_9 va2_13 va2_22 va2_32 vb1
>  age_1-age_5  smk_dico) a0(0) a1(1) m(1) yreg(logistic) mreg(logistic) nointer case

Iteration 0:   log likelihood = -6461.3363
Iteration 1:   log likelihood = -6096.4103
Iteration 2:   log likelihood = -6091.5848
Iteration 3:   log likelihood = -6091.5782

Logistic regression                                     Number of obs   =      10086
                                                        LR chi2(16)     =     739.52
                                                        Prob > chi2     =     0.0000
Log likelihood = -6091.5782                             Pseudo R2       =     0.0572

------------------------------------------------------------------------------
         va1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    ses_dico |  -.4598254   .0529631    -8.68   0.000    -.5636311   -.3560197
     vg2_new |   .9884914   .0776984    12.72   0.000     .8362053    1.140778
       va2_2 |   .2976286   .0893321     3.33   0.001      .122541    .4727163
       va2_5 |   .6033008   .0646006     9.34   0.000      .476686    .7299157
       va2_8 |   .2831627    .098767     2.87   0.004     .0895831    .4767424
       va2_9 |   .9051311   .0830952    10.89   0.000     .7422675    1.067995
      va2_13 |  -.1057111   .1178312    -0.90   0.370     -.336656    .1252338
      va2_22 |  -.1732004   .0751801    -2.30   0.021    -.3205507   -.0258501
      va2_32 |  -.0516461   .1208655    -0.43   0.669    -.2885381    .1852458
         vb1 |  -.0676743   .0520342    -1.30   0.193    -.1696594    .0343108
       age_1 |   .5534439   .0705008     7.85   0.000     .4152649    .6916229
       age_2 |    .658837   .0780806     8.44   0.000     .5058019    .8118721
       age_3 |   .7546822    .084119     8.97   0.000     .5898119    .9195525
       age_4 |   .7903938    .082398     9.59   0.000     .6288967    .9518909
       age_5 |   .7814204   .0971365     8.04   0.000     .5910363    .9718045
    smk_dico |   .1139019   .0509282     2.24   0.025     .0140845    .2137193
       _cons |  -1.313889   .1162034   -11.31   0.000    -1.541643   -1.086134
------------------------------------------------------------------------------

Iteration 0:   log likelihood = -1380.5431
Iteration 1:   log likelihood = -1298.0339
Iteration 2:   log likelihood = -1276.9076
Iteration 3:   log likelihood = -1276.3191
Iteration 4:   log likelihood = -1276.3156
Iteration 5:   log likelihood = -1276.3156

Logistic regression                                     Number of obs   =       6663
                                                        LR chi2(15)     =     208.45
                                                        Prob > chi2     =     0.0000
Log likelihood = -1276.3156                             Pseudo R2       =     0.0755

------------------------------------------------------------------------------
     vg2_new |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    ses_dico |  -.3337285   .1380889    -2.42   0.016    -.6043778   -.0630792
       va2_2 |  -1.390771   .4277827    -3.25   0.001    -2.229209   -.5523321
       va2_5 |  -.2667684   .1921354    -1.39   0.165    -.6433468      .10981
       va2_8 |  -.0205889   .2766695    -0.07   0.941    -.5628511    .5216733
       va2_9 |  -.1712079   .2886609    -0.59   0.553    -.7369729    .3945571
      va2_13 |   .1893558   .3016974     0.63   0.530    -.4019603    .7806719
      va2_22 |   .6389509   .1650293     3.87   0.000     .3154995    .9624024
```

```
      va2_32 |   .9545379   .2327809     4.10   0.000     .4982957     1.41078
         vb1 |  -.4708851   .1394776    -3.38   0.001    -.7442562    -.197514
       age_1 |   .4999147    .211236     2.37   0.018     .0858997    .9139296
       age_2 |   .8681748   .2188765     3.97   0.000     .4391848    1.297165
       age_3 |   .9416078    .231743     4.06   0.000     .4873999    1.395816
       age_4 |    1.06603   .2220013     4.80   0.000     .6309158    1.501145
       age_5 |   1.088583   .2338092     4.66   0.000     .6303253     1.54684
    smk_dico |   .4201382     .13064     3.22   0.001     .1640884     .676188
       _cons |  -3.199394   .3050865   -10.49   0.000    -3.797352   -2.601435
------------------------------------------------------------------------------

             |   Estimate     Std Err   P>|z|   [95% Conf   Interval]
-------------+----------------------------------------------------
         cde |  .63139387   .05296305   0.000   .56913763   .70046014
         nde |  .63139387   .05296305   0.000   .56913763   .70046014
         nie |  .97879397   .00880892   0.015   .96203966   .99584005
         mte |  .61800451   .05369854   0.000   .55626602    .6865952

cde:controlled direct effect, nde:natural direct effect, nie:natural indirect effect,
     mte:marginal total effect


. paramed va1, avar(ses_dico) mvar(vg8_new) cvars(va2_5  va2_9 va2_13 va2_32 vb1 age_1-age_5  smk_
> dico) a0(0) a1(1) m(1) yreg(logistic) mreg(logistic) nointer case

Iteration 0:   log likelihood = -4538.5335
Iteration 1:   log likelihood = -4259.5752
Iteration 2:   log likelihood = -4254.6498
Iteration 3:   log likelihood = -4254.6382

Logistic regression                               Number of obs   =       7040
                                                  LR chi2(13)     =     567.79
                                                  Prob > chi2     =     0.0000
Log likelihood = -4254.6382                       Pseudo R2       =     0.0626

------------------------------------------------------------------------------
         va1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    ses_dico |  -.4971973   .0644903    -7.71   0.000    -.6235959   -.3707986
     vg8_new |   .2596742   .1018385     2.55   0.011     .0600745     .459274
       va2_5 |    .547338    .065352     8.38   0.000     .4192505    .6754255
       va2_9 |   .9343806   .0856597    10.91   0.000     .7664906    1.102271
      va2_13 |  -.0946726   .1184949    -0.80   0.424    -.3269183     .137573
      va2_32 |   .0463506   .1238307     0.37   0.708    -.1963532    .2890543
         vb1 |  -.1976719   .0629412    -3.14   0.002    -.3210344   -.0743093
       age_1 |   .6284151    .082206     7.64   0.000     .4672942    .7895359
       age_2 |   .8892968   .0905964     9.82   0.000      .711731    1.066863
       age_3 |   .9114648   .0975249     9.35   0.000     .7203195     1.10261
       age_4 |   1.034202   .0961723    10.75   0.000     .8457073    1.222696
       age_5 |   .9095407   .1246505     7.30   0.000     .6652302    1.153851
    smk_dico |   .0461955   .0630348     0.73   0.464    -.0773505    .1697414
       _cons |  -1.147424   .1363367    -8.42   0.000    -1.41464   -.8802093
------------------------------------------------------------------------------

Iteration 0:   log likelihood = -1030.6692
Iteration 1:   log likelihood = -989.78874
Iteration 2:   log likelihood = -986.29117
Iteration 3:   log likelihood = -986.26368
Iteration 4:   log likelihood = -986.26367

Logistic regression                               Number of obs   =       4607
                                                  LR chi2(12)     =      88.81
                                                  Prob > chi2     =     0.0000
Log likelihood = -986.26367                       Pseudo R2       =     0.0431

------------------------------------------------------------------------------
     vg8_new |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    ses_dico |  -.2809581   .1449145    -1.94   0.053    -.5649853    .0030691
       va2_5 |   .4292715   .1550302     2.77   0.006     .1254178    .7331252
       va2_9 |  -.4028762   .2759516    -1.46   0.144    -.9437314    .1379791
      va2_13 |   .4649012     .23409     1.99   0.047     .0060932    .9237092
      va2_32 |   .0119995   .3017791     0.04   0.968    -.5794767    .6034758
         vb1 |  -.4131191    .161516    -2.56   0.011    -.7296847   -.0965535
       age_1 |   .2373884   .1838753     1.29   0.197    -.1230006    .5977773
       age_2 |   .3915244   .2093405     1.87   0.061    -.0187754    .8018243
       age_3 |   .3222319   .2353428     1.37   0.171    -.1390314    .7834953
       age_4 |   .2856504   .2351557     1.21   0.224    -.1752464    .7465471
```

```
       age_5 |  -.1264574   .3364219    -0.38   0.707    -.7858321    .5329174
    smk_dico |   .6344828   .1622263     3.91   0.000     .3165252    .9524405
       _cons |   -2.79933   .3274723    -8.55   0.000    -3.441164   -2.157496
------------------------------------------------------------------------------

             |   Estimate     Std Err   P>|z|   [95% Conf   Interval]
-------------+----------------------------------------------------
         cde |  .60823299   .06449029   0.000   .53601226   .69018452
         nde |  .60823299   .06449029   0.000   .53601226   .69018452
         nie |   .9960751   .00879351   0.655   .97905457   1.0133915
         mte |  .60584574   .06507067   0.000   .53330147    .6882581

cde:controlled direct effect, nde:natural direct effect, nie:natural indirect effect,
     mte:marginal total effect



paramed va1, avar(smk_dico) mvar(vg2_new) cvars(va2_2 va2_5 va2_8 va2_9 va2_13 va2_22 va2_32 vb1
>  age_1-age_5  ses_dico) a0(0) a1(1) m(1) yreg(logistic) mreg(logistic) nointer case

Iteration 0:   log likelihood = -6461.3363
Iteration 1:   log likelihood = -6096.4103
Iteration 2:   log likelihood = -6091.5848
Iteration 3:   log likelihood = -6091.5782

Logistic regression                                     Number of obs   =      10086
                                                        LR chi2(16)     =     739.52
                                                        Prob > chi2     =     0.0000
Log likelihood = -6091.5782                             Pseudo R2       =     0.0572

------------------------------------------------------------------------------
         va1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    smk_dico |   .1139019   .0509282     2.24   0.025     .0140845    .2137193
     vg2_new |   .9884914   .0776984    12.72   0.000     .8362053    1.140778
       va2_2 |   .2976286   .0893321     3.33   0.001      .122541    .4727163
       va2_5 |   .6033008   .0646006     9.34   0.000      .476686    .7299157
       va2_8 |   .2831627    .098767     2.87   0.004     .0895831    .4767424
       va2_9 |   .9051311   .0830952    10.89   0.000     .7422675    1.067995
      va2_13 |  -.1057111   .1178312    -0.90   0.370     -.336656    .1252338
      va2_22 |  -.1732004   .0751801    -2.30   0.021    -.3205507   -.0258501
      va2_32 |  -.0516461   .1208655    -0.43   0.669    -.2885381    .1852458
         vb1 |  -.0676743   .0520342    -1.30   0.193    -.1696594    .0343108
       age_1 |   .5534439   .0705008     7.85   0.000     .4152649    .6916229
       age_2 |    .658837   .0780806     8.44   0.000     .5058019    .8118721
       age_3 |   .7546822    .084119     8.97   0.000     .5898119    .9195525
       age_4 |   .7903938    .082398     9.59   0.000     .6288967    .9518909
       age_5 |   .7814204   .0971365     8.04   0.000     .5910363    .9718045
    ses_dico |  -.4598254   .0529631    -8.68   0.000    -.5636311   -.3560197
       _cons |  -1.313889   .1162034   -11.31   0.000    -1.541643   -1.086134
------------------------------------------------------------------------------

Iteration 0:   log likelihood = -1380.5431
Iteration 1:   log likelihood = -1298.0339
Iteration 2:   log likelihood = -1276.9076
Iteration 3:   log likelihood = -1276.3191
Iteration 4:   log likelihood = -1276.3156
Iteration 5:   log likelihood = -1276.3156

Logistic regression                                     Number of obs   =       6663
                                                        LR chi2(15)     =     208.45
                                                        Prob > chi2     =     0.0000
Log likelihood = -1276.3156                             Pseudo R2       =     0.0755

------------------------------------------------------------------------------
     vg2_new |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    smk_dico |   .4201382     .13064     3.22   0.001     .1640884     .676188
       va2_2 |  -1.390771   .4277827    -3.25   0.001    -2.229209   -.5523321
       va2_5 |  -.2667684   .1921354    -1.39   0.165    -.6433468      .10981
       va2_8 |  -.0205889   .2766695    -0.07   0.941    -.5628511    .5216733
       va2_9 |  -.1712079   .2886609    -0.59   0.553    -.7369729    .3945571
      va2_13 |   .1893558   .3016974     0.63   0.530    -.4019603    .7806719
      va2_22 |   .6389509   .1650293     3.87   0.000     .3154995    .9624024
      va2_32 |   .9545379   .2327809     4.10   0.000     .4982957     1.41078
         vb1 |  -.4708851   .1394776    -3.38   0.001    -.7442562    -.197514
       age_1 |   .4999147    .211236     2.37   0.018     .0858997    .9139296
       age_2 |   .8681748   .2188765     3.97   0.000     .4391848    1.297165
```

```
       age_3 |   .9416078    .231743     4.06   0.000     .4873999    1.395816
       age_4 |    1.06603   .2220013     4.80   0.000     .6309158    1.501145
       age_5 |   1.088583   .2338092     4.66   0.000     .6303253     1.54684
    ses_dico |  -.3337285   .1380889    -2.42   0.016    -.6043778   -.0630792
       _cons |  -3.199394   .3050865   -10.49   0.000    -3.797352   -2.601435
------------------------------------------------------------------------------

             |   Estimate     Std Err   P>|z|   [95% Conf   Interval]
-------------+----------------------------------------------------
         cde |  1.1206422   .05092817   0.025   1.0141823   1.2382773
         nde |  1.1206422   .05092817   0.025   1.0141823   1.2382773
         nie |  1.0273119   .00485971   0.000   1.0175732   1.0371438
         mte |  1.1512491   .05096957   0.006    1.041797   1.2722002

cde:controlled direct effect, nde:natural direct effect, nie:natural indirect effect,
     mte:marginal total effect

. paramed va1, avar(smk_dico) mvar(vg8_new) cvars(va2_5  va2_9 va2_13 va2_32 vb1 age_1-age_5  ses_
> dico) a0(0) a1(1) m(1) yreg(logistic) mreg(logistic) nointer case

Iteration 0:   log likelihood = -4538.5335
Iteration 1:   log likelihood = -4259.5752
Iteration 2:   log likelihood = -4254.6498
Iteration 3:   log likelihood = -4254.6382

Logistic regression                               Number of obs   =       7040
                                                  LR chi2(13)     =     567.79
                                                  Prob > chi2     =     0.0000
Log likelihood = -4254.6382                       Pseudo R2       =     0.0626

------------------------------------------------------------------------------
         va1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    smk_dico |   .0461955   .0630348     0.73   0.464    -.0773505    .1697414
     vg8_new |   .2596742   .1018385     2.55   0.011     .0600745     .459274
       va2_5 |    .547338    .065352     8.38   0.000     .4192505    .6754255
       va2_9 |   .9343806   .0856597    10.91   0.000     .7664906    1.102271
      va2_13 |  -.0946726   .1184949    -0.80   0.424    -.3269183     .137573
      va2_32 |   .0463506   .1238307     0.37   0.708    -.1963532    .2890543
         vb1 |  -.1976719   .0629412    -3.14   0.002    -.3210344   -.0743093
       age_1 |   .6284151    .082206     7.64   0.000     .4672942    .7895359
       age_2 |   .8892968   .0905964     9.82   0.000      .711731    1.066863
       age_3 |   .9114648   .0975249     9.35   0.000     .7203195     1.10261
       age_4 |   1.034202   .0961723    10.75   0.000     .8457073    1.222696
       age_5 |   .9095407   .1246505     7.30   0.000     .6652302    1.153851
    ses_dico |  -.4971973   .0644903    -7.71   0.000    -.6235959   -.3707986
       _cons |  -1.147424   .1363367    -8.42   0.000     -1.41464   -.8802093
------------------------------------------------------------------------------

Iteration 0:   log likelihood = -1030.6692
Iteration 1:   log likelihood = -989.78874
Iteration 2:   log likelihood = -986.29117
Iteration 3:   log likelihood = -986.26368
Iteration 4:   log likelihood = -986.26367

Logistic regression                               Number of obs   =       4607
                                                  LR chi2(12)     =      88.81
                                                  Prob > chi2     =     0.0000
Log likelihood = -986.26367                       Pseudo R2       =     0.0431

------------------------------------------------------------------------------
     vg8_new |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    smk_dico |   .6344828   .1622263     3.91   0.000     .3165252    .9524405
       va2_5 |   .4292715   .1550302     2.77   0.006     .1254178    .7331252
       va2_9 |  -.4028762   .2759516    -1.46   0.144    -.9437314    .1379791
      va2_13 |   .4649012     .23409     1.99   0.047     .0060932    .9237092
      va2_32 |   .0119995   .3017791     0.04   0.968    -.5794767    .6034758
         vb1 |  -.4131191    .161516    -2.56   0.011    -.7296847   -.0965535
       age_1 |   .2373884   .1838753     1.29   0.197    -.1230006    .5977773
       age_2 |   .3915244   .2093405     1.87   0.061    -.0187754    .8018243
       age_3 |   .3222319   .2353428     1.37   0.171    -.1390314    .7834953
       age_4 |   .2856504   .2351557     1.21   0.224    -.1752464    .7465471
       age_5 |  -.1264574   .3364219    -0.38   0.707    -.7858321    .5329174
    ses_dico |  -.2809581   .1449145    -1.94   0.053    -.5649853    .0030691
       _cons |   -2.79933   .3274723    -8.55   0.000    -3.441164   -2.157496
------------------------------------------------------------------------------
```

```
             |   Estimate     Std Err   P>|z|   [95% Conf   Interval]
-------------+----------------------------------------------------
         cde |  1.0472791   .06303482   0.464   .92556328   1.1850011
         nde |  1.0472791   .06303482   0.464   .92556328   1.1850011
         nie |  1.0088856   .00675616   0.190   .99561393   1.0223342
         mte |  1.0565848    .0631693   0.384   .93354138   1.1958457

cde:controlled direct effect, nde:natural direct effect, nie:natural indirect effect,
     mte:marginal total effect


. paramed va1, avar(vi4_dico) mvar(vg2_new) cvars(va2_2 va2_8 va2_9 va2_13 va2_32 vb1 age_1-age_5
>  smk_dico ses_dico) a0(0) a1(1) m(1) yreg(logistic) mreg(logistic) nointer case

Iteration 0:   log likelihood = -3855.8775
Iteration 1:   log likelihood = -3597.5888
Iteration 2:   log likelihood = -3592.5602
Iteration 3:   log likelihood = -3592.5505
Iteration 4:   log likelihood = -3592.5505

Logistic regression                               Number of obs   =       6281
                                                  LR chi2(15)     =     526.65
                                                  Prob > chi2     =     0.0000
Log likelihood = -3592.5505                       Pseudo R2       =     0.0683

------------------------------------------------------------------------------
         va1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    vi4_dico |   .2853578   .0733232     3.89   0.000      .141647    .4290686
     vg2_new |   1.087992   .1096149     9.93   0.000     .8731509    1.302833
       va2_2 |   .3095366    .090868     3.41   0.001     .1314385    .4876347
       va2_8 |   .2429938    .101349     2.40   0.017     .0443535    .4416342
       va2_9 |   .8674714   .0874722     9.92   0.000      .696029    1.038914
      va2_13 |   .0559256   .1329433     0.42   0.674    -.2046385    .3164898
      va2_32 |  -.1859439   .1365333    -1.36   0.173    -.4535443    .0816565
         vb1 |  -.0951544   .0689367    -1.38   0.167    -.2302679    .0399592
       age_1 |   .5931147   .0833023     7.12   0.000     .4298453    .7563841
       age_2 |   .8805371   .0957957     9.19   0.000     .6927809    1.068293
       age_3 |   1.034119   .1050092     9.85   0.000     .8283046    1.239933
       age_4 |   1.361576   .1133381    12.01   0.000     1.139438    1.583715
       age_5 |   1.170516   .1418112     8.25   0.000     .8925709    1.448461
    smk_dico |   .0960447   .0664831     1.44   0.149    -.0342598    .2263491
    ses_dico |  -.3947094   .0677302    -5.83   0.000    -.5274581   -.2619607
       _cons |  -1.690721   .1625565   -10.40   0.000    -2.009326   -1.372116
------------------------------------------------------------------------------

Iteration 0:   log likelihood = -741.05859
Iteration 1:   log likelihood = -715.15882
Iteration 2:   log likelihood =  -691.3259
Iteration 3:   log likelihood = -690.40181
Iteration 4:   log likelihood = -690.39724

Logistic regression                               Number of obs   =       4374
                                                  LR chi2(14)     =     101.32
                                                  Prob > chi2     =     0.0000
Log likelihood = -690.39724                       Pseudo R2       =     0.0684

------------------------------------------------------------------------------
     vg2_new |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    vi4_dico |   .3101589   .1973327     1.57   0.116    -.0766061     .696924
       va2_2 |  -1.472699   .4289365    -3.43   0.001    -2.313399   -.6319993
       va2_8 |  -.0968441   .2858214    -0.34   0.735    -.6570438    .4633556
       va2_9 |  -.1715206   .2962574    -0.58   0.563    -.7521745    .4091333
      va2_13 |   .4128174   .3253956     1.27   0.205    -.2249462    1.050581
      va2_32 |   .9594726   .2751005     3.49   0.000     .4202855     1.49866
         vb1 |  -.6532123   .1983965    -3.29   0.001    -1.042062   -.2643624
       age_1 |   .5726352   .2306808     2.48   0.013     .1205091    1.024761
       age_2 |   .6828209   .2734786     2.50   0.013     .1468126    1.218829
       age_3 |   .7416613   .3009531     2.46   0.014     .1518042    1.331519
       age_4 |   .8102438   .3283959     2.47   0.014     .1665996    1.453888
       age_5 |   1.203173   .3132669     3.84   0.000     .5891811    1.817165
    smk_dico |   .2762066   .1805898     1.53   0.126    -.0777429    .6301561
    ses_dico |   -.300285   .1855224    -1.62   0.106    -.6639022    .0633321
       _cons |  -3.082194   .4342167    -7.10   0.000    -3.933243   -2.231144
------------------------------------------------------------------------------

             |   Estimate     Std Err   P>|z|   [95% Conf   Interval]
```

```
-------------+------------------------------------------------------------
         cde |  1.3302379   .07332317   0.000   1.1521669   1.5358304
         nde |  1.3302379   .07332317   0.000   1.1521669   1.5358304
         nie |  1.0208741    .0067744   0.002   1.0074087   1.0345194
         mte |  1.3580054   .07363803   0.000   1.1754916   1.5688573

cde:controlled direct effect, nde:natural direct effect, nie:natural indirect effect,
     mte:marginal total effect

. paramed va1, avar(vi4_dico) mvar(vg8_new) cvars(va2_9 va2_13 va2_32 vb1 age_1-age_5  smk_dico se
> s_dico) a0(0) a1(1) m(1) yreg(logistic) mreg(logistic) nointer case

Iteration 0:   log likelihood = -2983.3916
Iteration 1:   log likelihood = -2758.7881
Iteration 2:   log likelihood = -2752.7448
Iteration 3:   log likelihood = -2752.7211
Iteration 4:   log likelihood = -2752.7211

Logistic regression                                     Number of obs   =       4906
                                                        LR chi2(13)     =     461.34
                                                        Prob > chi2     =     0.0000
Log likelihood = -2752.7211                             Pseudo R2       =     0.0773

------------------------------------------------------------------------------
         va1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    vi4_dico |     .40281   .0812395     4.96   0.000     .2435836    .5620365
     vg8_new |    .519688   .1342888     3.87   0.000     .2564868    .7828893
       va2_9 |   .9153031   .0915622    10.00   0.000     .7358444    1.094762
      va2_13 |   .1531701   .1355183     1.13   0.258    -.1124408     .418781
      va2_32 |  -.0843437   .1389394    -0.61   0.544      -.35666    .1879726
         vb1 |   -.183742   .0783696    -2.34   0.019    -.3373435   -.0301404
       age_1 |   .7352974   .0977369     7.52   0.000     .5437367    .9268581
       age_2 |   1.139174   .1104193    10.32   0.000      .922756    1.355592
       age_3 |   1.260102    .118319    10.65   0.000     1.028202    1.492003
       age_4 |   1.604715   .1263707    12.70   0.000     1.357033    1.852397
       age_5 |   1.440458    .157164     9.17   0.000     1.132422    1.748494
    smk_dico |   .0702384   .0778111     0.90   0.367    -.0822685    .2227453
    ses_dico |  -.4383125   .0815557    -5.37   0.000    -.5981588   -.2784662
       _cons |  -1.757716   .1843453    -9.53   0.000    -2.119027   -1.396406
------------------------------------------------------------------------------

Iteration 0:   log likelihood = -656.62513
Iteration 1:   log likelihood = -632.50927
Iteration 2:   log likelihood = -630.65798
Iteration 3:   log likelihood = -630.64577
Iteration 4:   log likelihood = -630.64577

Logistic regression                                     Number of obs   =       3450
                                                        LR chi2(12)     =      51.96
                                                        Prob > chi2     =     0.0000
Log likelihood = -630.64577                             Pseudo R2       =     0.0396

------------------------------------------------------------------------------
     vg8_new |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    vi4_dico |  -.0422919   .2019998    -0.21   0.834    -.4382042    .3536204
       va2_9 |  -.3581313   .2827846    -1.27   0.205     -.912379    .1961164
      va2_13 |   .3485041   .2790668     1.25   0.212    -.1984566    .8954649
      va2_32 |  -.1065812   .3493886    -0.31   0.760    -.7913703    .5782079
         vb1 |  -.6292612   .2084543    -3.02   0.003    -1.037824   -.2206984
       age_1 |   .1708381   .2094623     0.82   0.415    -.2397005    .5813767
       age_2 |    .371167   .2537957     1.46   0.144    -.1262635    .8685975
       age_3 |   .1543446   .3090167     0.50   0.617     -.451317    .7600063
       age_4 |   .2214821   .3496923     0.63   0.526    -.4639021    .9068664
       age_5 |  -.0672292   .4533939    -0.15   0.882     -.955865    .8214065
    smk_dico |   .6117039   .1978869     3.09   0.002     .2238527     .999555
    ses_dico |  -.3562854   .1839782    -1.94   0.053    -.7168759    .0043052
       _cons |  -2.392815   .4419131    -5.41   0.000    -3.258949   -1.526681
------------------------------------------------------------------------------

             |   Estimate     Std Err   P>|z|   [95% Conf   Interval]
-------------+------------------------------------------------------------
         cde |  1.4960227    .0812395   0.000   1.2758092   1.7542466
         nde |  1.4960227    .0812395   0.000   1.2758092   1.7542466
         nie |   .9987305   .00991574   0.898   .97950773   1.0183305
         mte |  1.4941235   .08183997   0.000   1.2726908   1.7540828
```

```
cde:controlled direct effect, nde:natural direct effect, nie:natural indirect effect,
     mte:marginal total effect
```

```
. paramed va1, avar(alcolextreme) mvar(vg2_new) cvars(va2_2 va2_5 va2_9 va2_22 va2_32 vb1 age_1-ag
> e_5  smk_dico ses_dico) a0(0) a1(1) m(1) yreg(logistic) mreg(logistic) nointer case

Iteration 0:   log likelihood = -6080.9855
Iteration 1:   log likelihood = -5770.2383
Iteration 2:   log likelihood = -5767.0842
Iteration 3:   log likelihood = -5767.0817

Logistic regression                               Number of obs   =       9443
                                                  LR chi2(15)     =     627.81
                                                  Prob > chi2     =     0.0000
Log likelihood = -5767.0817                       Pseudo R2       =     0.0516

------------------------------------------------------------------------------
         va1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
alcolextreme |   .1242137   .0723116     1.72   0.086    -.0175145    .2659418
     vg2_new |   1.006378   .0791119    12.72   0.000     .8513217    1.161435
       va2_2 |   .2922023   .0889104     3.29   0.001     .1179411    .4664635
       va2_5 |   .6194822   .0650773     9.52   0.000      .491933    .7470314
       va2_9 |   .7895022   .0828921     9.52   0.000     .6270366    .9519678
      va2_22 |  -.1500276   .0759543    -1.98   0.048    -.2988952   -.0011599
      va2_32 |  -.1124672   .1192708    -0.94   0.346    -.3462338    .1212993
         vb1 |  -.0197597   .0546953    -0.36   0.718    -.1269605    .0874412
       age_1 |   .4861201   .0729614     6.66   0.000     .3431185    .6291218
       age_2 |   .5568256   .0803142     6.93   0.000     .3994126    .7142385
       age_3 |   .6808029   .0863338     7.89   0.000     .5115918    .8500141
       age_4 |   .7035353   .0844826     8.33   0.000     .5379524    .8691183
       age_5 |   .7234687   .0987689     7.32   0.000     .5298852    .9170521
    smk_dico |   .0807252   .0520542     1.55   0.121    -.0212991    .1827496
    ses_dico |  -.4087522    .054157    -7.55   0.000    -.5148979   -.3026065
       _cons |  -1.315283   .1232179   -10.67   0.000    -1.556786   -1.073781
------------------------------------------------------------------------------

Iteration 0:   log likelihood =  -1311.383
Iteration 1:   log likelihood = -1230.6812
Iteration 2:   log likelihood = -1210.2069
Iteration 3:   log likelihood = -1209.6171
Iteration 4:   log likelihood = -1209.6129
Iteration 5:   log likelihood = -1209.6129

Logistic regression                               Number of obs   =       6190
                                                  LR chi2(14)     =     203.54
                                                  Prob > chi2     =     0.0000
Log likelihood = -1209.6129                       Pseudo R2       =     0.0776

------------------------------------------------------------------------------
     vg2_new |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
alcolextreme |  -.1061408   .1915548    -0.55   0.580    -.4815814    .2692997
       va2_2 |  -1.410096   .4281645    -3.29   0.001    -2.249283   -.5709085
       va2_5 |  -.3140577   .1942376    -1.62   0.106    -.6947563    .0666409
       va2_9 |  -.1189551   .2879507    -0.41   0.680     -.683328    .4454179
      va2_22 |    .617429   .1669592     3.70   0.000     .2901949     .944663
      va2_32 |   .9731402   .2270196     4.29   0.000       .52819     1.41809
         vb1 |  -.4281589   .1430575    -2.99   0.003    -.7085465   -.1477714
       age_1 |   .4527043   .2255968     2.01   0.045     .0105426    .8948659
       age_2 |   .8632918   .2273709     3.80   0.000      .417653    1.308931
       age_3 |   .9617959   .2401208     4.01   0.000     .4911677    1.432424
       age_4 |   1.059109   .2305728     4.59   0.000     .6071949    1.511024
       age_5 |   1.087456    .240917     4.51   0.000     .6152678    1.559645
    smk_dico |    .433427   .1333577     3.25   0.001     .1720506    .6948033
    ses_dico |  -.3769077   .1423706    -2.65   0.008    -.6559491   -.0978664
       _cons |  -3.196732   .3221518    -9.92   0.000    -3.828138   -2.565327
------------------------------------------------------------------------------

             |   Estimate     Std Err   P>|z|   [95% Conf   Interval]
-------------+-----------------------------------------------------
         cde |  1.1322578   .07231159   0.086   .98263546   1.3046625
         nde |  1.1322578   .07231159   0.086   .98263546   1.3046625
         nie |  .99311322   .00942453   0.463   .97493674   1.0116286
```

```
        mte |  1.1244601   .07291317   0.108   .97471832   1.2972062

cde:controlled direct effect, nde:natural direct effect, nie:natural indirect effect,
     mte:marginal total effect

. paramed va1, avar(alcolextreme) mvar(vg8_new) cvars(va2_5 va2_9 va2_32 vb1 age_1-age_5  smk_dico
>  ses_dico) a0(0) a1(1) m(1) yreg(logistic) mreg(logistic) nointer case

Iteration 0:   log likelihood = -4219.8435
Iteration 1:   log likelihood = -3993.8098
Iteration 2:   log likelihood = -3990.7027
Iteration 3:   log likelihood = -3990.6982

Logistic regression                               Number of obs   =       6494
                                                  LR chi2(13)     =     458.29
                                                  Prob > chi2     =     0.0000
Log likelihood = -3990.6982                       Pseudo R2       =     0.0543

------------------------------------------------------------------------------
         va1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
alcolextreme |   .1035541   .0777116     1.33   0.183    -.0487578     .255866
     vg8_new |   .3075654   .1042362     2.95   0.003     .1032662    .5118645
       va2_5 |   .6064512    .070028     8.66   0.000     .4691988    .7437036
       va2_9 |   .8830951   .0878795    10.05   0.000     .7108545    1.055336
      va2_32 |   .0644592   .1243576     0.52   0.604    -.1792773    .3081956
         vb1 |  -.1340093   .0677625    -1.98   0.048    -.2668213   -.0011972
       age_1 |   .5178988    .085764     6.04   0.000     .3498045     .685993
       age_2 |   .7410929   .0935282     7.92   0.000     .5577809    .9244049
       age_3 |   .8095662   .1001988     8.08   0.000     .6131801    1.005952
       age_4 |   .8972371   .0989048     9.07   0.000     .7033872    1.091087
       age_5 |   .7913447   .1265945     6.25   0.000      .543224    1.039465
    smk_dico |   .0161131   .0647898     0.25   0.804    -.1108725    .1430987
    ses_dico |  -.4721425   .0665933    -7.09   0.000     -.602663    -.341622
       _cons |  -1.170355   .1491475    -7.85   0.000    -1.462679   -.8780314
------------------------------------------------------------------------------

Iteration 0:   log likelihood = -930.87534
Iteration 1:   log likelihood = -889.87334
Iteration 2:   log likelihood = -885.99097
Iteration 3:   log likelihood = -885.95437
Iteration 4:   log likelihood = -885.95436

Logistic regression                               Number of obs   =       4196
                                                  LR chi2(12)     =      89.84
                                                  Prob > chi2     =     0.0000
Log likelihood = -885.95436                       Pseudo R2       =     0.0483

------------------------------------------------------------------------------
     vg8_new |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
alcolextreme |   .2278877   .1860424     1.22   0.221    -.1367488    .5925241
       va2_5 |   .4772503   .1718116     2.78   0.005     .1405057    .8139949
       va2_9 |  -.4439282   .2879528    -1.54   0.123    -1.008305    .1204489
      va2_32 |   .0749905   .3054363     0.25   0.806    -.5236537    .6736347
         vb1 |  -.3641192   .1753208    -2.08   0.038    -.7077416   -.0204968
       age_1 |   .4005511   .2045729     1.96   0.050    -.0004045    .8015067
       age_2 |   .4933508   .2255638     2.19   0.029     .0512538    .9354477
       age_3 |   .4318767   .2538086     1.70   0.089     -.065579    .9293325
       age_4 |   .4392584   .2494471     1.76   0.078     -.049649    .9281657
       age_5 |   .0026426   .3466022     0.01   0.994    -.6766853    .6819705
    smk_dico |   .6142024   .1713953     3.58   0.000     .2782738    .9501311
    ses_dico |  -.3622572   .1548302    -2.34   0.019    -.6657188   -.0587956
       _cons |  -2.998624    .368012    -8.15   0.000    -3.719914   -2.277334
------------------------------------------------------------------------------

             |   Estimate     Std Err   P>|z|   [95% Conf   Interval]
-------------+------------------------------------------------------
         cde |  1.1091058   .07771157   0.183   .95240912   1.2915832
         nde |  1.1091058   .07771157   0.183   .95240912   1.2915832
         nie |   1.004033   .00848977   0.635   .98746421   1.0208799
         mte |  1.1135788   .07819049   0.169   .95535301   1.2980101

cde:controlled direct effect, nde:natural direct effect, nie:natural indirect effect,
     mte:marginal total effect
```