

1 Exposure to ambient air pollution and elevated blood levels of gamma-glutamyl transferase in a
2 large Austrian cohort

3 Authors:

4

5 Jan Wirsching,¹ Gabriele Nagel,^{1,2} Ming-Yi Tsai,³ Kees de Hoogh^{4,5}, Andrea Jaensch,¹ Bernhard
6 Anwander⁶, Ranjeet S Sokhi⁷, Hanno Ulmer⁸, Emanuel Zitt^{2,9}, Hans Concini², Bert Brunekreef,^{10,11} Gerard
7 Hoek,¹⁰ and Gudrun Weinmayr.^{1*}

8

9 **Affiliations:**

10 ¹Institute of Epidemiology and Medical Biometry, Ulm University, Ulm;

11 ²Agency for Preventive and Social Medicine, Bregenz (aks), Austria;

12 ³Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, USA;

13 ⁴Swiss Tropical and Public Health Institute, Basel, Switzerland

14 ⁵ University of Basel, Basel, Switzerland

15 ⁶ Institut für Umwelt und Lebensmittelsicherheit des Landes Vorarlberg, Bregenz, Austria

16 ⁷Centre for Atmospheric and Climate Physics Research (CACP), School of Physics, Astronomy and Mathematics, University of
17 Hertfordshire, Hatfield, UK

18 ⁸ Department of Medical Statistics, Informatics and Health Economics, Medical University of Innsbruck, Innsbruck, Austria

19 ⁹Department of Internal Medicine 3, LKH Feldkirch, Feldkirch, Austria;

20 ¹⁰Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands;

21 ¹¹Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands.

22

23 * Correspondence to: Gudrun Weinmayr, Institute of Epidemiology and Medical Biometry, Ulm
24 University, Helmholtzstr.22, 89081 Ulm, Germany, Telephone: +49-731-50-31071, Fax: +49-731-50-
25 31069, E-Mail: gudrun.weinmayr@uni-ulm.de

26

27 **Abstract**

28 Gamma glutamyl transferase (GGT) is related to oxidative stress and an indicator for liver
29 damage. We investigated the association between air pollution and GGT in a large Austrian
30 cohort (N=116,109) to better understand how air pollution affects human health.

31 Data come from voluntary prevention visits that were routinely collected within the Vorarlberg
32 Health Monitoring and Prevention Program (VHM&PP). Recruitment was ongoing from 1985 to
33 2005. Blood was drawn and GGT measured centralized in two laboratories. Land use
34 regression models were applied to estimate individuals' exposure at their home address for
35 particulate matter (PM) with a diameter of less than 2.5 μm (PM_{2.5}), 10 μm (PM₁₀), fraction
36 between 10 μm and 2.5 μm (PM_{coarse}), as well as PM_{2.5} absorbance (PM_{2.5abs}), NO₂, NO_x
37 and eight components of PM. Linear regression modeling, adjusting for relevant individual and
38 community-level confounders were calculated.

39 The study population was 56% female with a mean age of 42 years and mean GGT was 19.0
40 units. Individual PM_{2.5} and NO₂ exposures were essentially below European limit values of 25
41 and 40 $\mu\text{g}/\text{m}^3$, respectively, with means of 13.58 $\mu\text{g}/\text{m}^3$ for PM_{2.5} and 19.93 $\mu\text{g}/\text{m}^3$ for NO₂.
42 Positive associations were observed for PM_{2.5}, PM₁₀, PM_{2.5abs}, NO₂, NO_x, and Cu, K, S in
43 PM_{2.5} and PM₁₀ fractions and Zn mainly in PM_{2.5} fraction. The strongest association per
44 interquartile range observed was an increase of serum GGT concentration by 1.40% (95%-CI:
45 0.85%; 1.95%) per 45.7 ng/m³ S in PM_{2.5}. Associations were robust to adjustments for other
46 biomarkers, in two-pollutant models and the subset with a stable residential history.

47 We found that long-term exposure to air pollution (PM_{2.5}, PM₁₀, PM_{2.5abs}, NO₂, NO_x) as well
48 as certain elements, were positively associated with baseline GGT levels. The elements
49 associated suggest a role of traffic emissions, long range transport and wood burning

50 Max. 300 words now 293 words

51 **Keywords:** GGT, nitrogen oxides, particulate matter, long-term exposure, sources, chemical
52 elements

53 1. INTRODUCTION

54 Air pollution is associated with a variety of adverse health effects in studies conducted all
55 around the world. Recent studies indicated associations between air pollution and cardio-
56 vascular disease (Brook et al., 2010; Mills et al., 2009; Yang et al., 2018), adverse respiratory
57 effects (Liu et al., 2017) , lung cancer (Ciabattini et al., 2021; Hamra et al., 2015) all-cause
58 mortality (Chen and Hoek, 2020; Huangfu and Atkinson, 2020) diabetes mellitus type 2
59 (Weinmayr et al., 2015; Yang et al., 2020) and liver cirrhosis (Orioli et al., 2019). Main proposed
60 mechanisms for these effects are systemic inflammation, resulting from an increase in oxidative
61 stress (Anderson et al., 2012). Gamma glutamyl transferase (GGT) is a ubiquitous enzyme
62 mostly expressed in liver and kidney. It is involved in the breakdown of glutathione (GSH) and is
63 a key player in GSH-associated biotransformation-processes, taking part in detoxification of
64 xenobiotics (Morris et al., 2014; Whitfield, 2001). GGT has also been ascribed pro-oxidant
65 properties, ensuing from the cleavage of extracellular glutathione and leading to promotion of
66 free radicals and oxidative stress (Corti et al., 2020; Lim et al., 2004). It was introduced into
67 clinical practice as a sensitive but not specific maker for (alcohol induced) liver damage
68 (Teschke et al., 1977) and is also elevated in non-alcoholic fatty liver disease (NAFLD) (van
69 Hoek, 2004). Air pollution has been hypothesized to be related to NAFLD including non-
70 alcoholic steatohepatitis (NASH) via pro-inflammatory cytokines and Kupffer cell activation (Kim
71 et al., 2014), which might result in liver cirrhosis and hepatocellular carcinoma.

72 Furthermore, baseline measurements of GGT have been proven to be a valuable predictive
73 biomarker for several pathologic conditions, including cardiovascular disease (CVD), diabetes
74 and metabolic syndrome (MetS) (Koenig and Seneff, 2015). From epidemiological studies there
75 is some evidence for a positive association between air pollution and GGT concentration. The
76 KORA study in Augsburg, Germany, investigated cross-sectional associations of long-term air
77 pollution with liver enzymes and showed a positive association between particulate matter with
78 diameter $<2.5\mu\text{m}$ (PM_{2.5}) and GGT (Markevych et al., 2013). A cross- sectional study in Taiwan
79 revealed that long-term exposure to PM_{2.5} was associated with increased levels of GGT
80 (Zhang et al., 2019).

81 The general mixture of PM is largely unknown and depends on the area where measurements
82 are conducted and the sources of PM in that area. An increase in the sulfur component has
83 been associated with natural mortality (Beelen et al., 2015). However, the exact mechanisms to
84 explain the impact of sulfur on human health is unknown. Sulfate may affect health indirectly by
85 solubilizing divalent metals altering bioavailability and enhancing oxidative stress (Kelly and

86 Fussell, 2012; Maciejczyk et al., 2021), and forming secondary organic PM (Kelly and Fussell,
87 2012). For example, upregulated GGT may increase glutathione breakdown and cysteinyl-
88 glycine, a product of this break down, is capable of reducing Fe(II) to Fe(III), initiating the
89 Fenton's reaction and therefore contributing to oxidative stress through formation of superoxide
90 anions, which react with water to form hydrogen peroxide (Dominici et al., 2005; Paolicchi et al.,
91 2002). In more general terms, intra-tracheal instillation of mice with insoluble particles
92 containing enriched Ti, V, Ni, Zn, Pb, Cr, and Cu have been found to induce inflammatory
93 signaling and cytokines upregulation in the liver leading to an abnormal liver function (Yuan et
94 al., 2021).

95 Regarding NO₂, it could be demonstrated, that exposure leads to an increase in GGT
96 expression in Jc1:Wistar rats, but little is known on the long term effects of NO₂ (Takahashi et
97 al., 1997). However, in patients with schizophrenia long-term exposure to NO₂ was found to
98 increase GGT levels, partly through alteration of the microbiome (Yi et al., 2021).

99 Because GGT is an indicator for liver and also associated with other disease, and furthermore
100 plays a role in detoxification and oxidative stress, we investigated whether exposure to air
101 pollution parameters (PM and nitric oxides) is positively associated with elevated plasma GGT
102 levels. In addition, we investigated chemical elements in PM that represent different exposure
103 sources. Furthermore, we hypothesize that certain elements, especially divalent metals and
104 sulfur play a crucial role in observed associations of PM with health, and therefore also with
105 GGT. These effects will be investigated in a large Austrian cohort.

106 2. METHODS

107 2.1. Study population and data acquisition

108 Between January 1985 and June 2005, more than 180.000 adult Vorarlberg residents (53.9%
109 female) were enrolled in the Vorarlberg Health Monitoring and Prevention Program (VHM&PP)
110 study cohort (Ulmer et al., 2007). Vorarlberg is the most western region ("state") of Austria and
111 the study population corresponds to approximately 2/3 of the total population of Vorarlberg.
112 Participants took part in a voluntary population-based medical prevention program offered once
113 a year for each adult inhabitant in Vorarlberg (Ulmer et al., 2007) and part of the participants
114 had one or more visits. In this study, we used the data of the first visit and the corresponding
115 address data that had been collected and that were transmitted with an anonymized identifying
116 number. During a medical examination the body mass index (BMI) (in kg/m²) was determined,
117 blood pressure was measured and a blood sample was drawn. Baseline serum levels of

118 glucose, triglycerides (TG), total cholesterol (TC) (all in mg/dl) and GGT (in U/L) were
119 determined.

120 GGT was measured centralized in two laboratories with intra-laboratory coefficients of variation
121 (CV) ranging from 3.3% to 0.8% and inter-laboratory CVs ranging from 13.8% to 5.5%. Detailed
122 measurement procedures for the outcome GGT are described elsewhere (Ruttmann et al.,
123 2005). A range of relevant potential confounders that are directly or indirectly linked to GGT was
124 considered: Standardized questionnaires were used to assess smoking status (never/ former/
125 current), and marital status (single/ married or living with partner/ divorced or separated/
126 widowed). Data on individual socioeconomic status (SES), namely occupational class
127 (white/blue collar classification or others), occupational status (employed/ unemployed/ retired
128 or receiving pension), was available from social security data. Variables for mean income (in
129 Euro), average unemployment (in %) and indicator for urbanicity (urban vs. rural; EUROSTAT
130 classification (Koceva et al., 2016)) were used to assess the neighborhood SES (Beelen et al.,
131 2014). These variables are correlated with liver disease and partly to alcohol consumption that
132 GGT is a marker of and can be related to air pollution mainly through socioeconomic status and
133 therefore qualify as potential confounders.

134 The present study conforms to the ethical guidelines of the 1975 Declaration of Helsinki and has
135 been approved by the Ethics Committee of Vorarlberg, Austria (EK-Nr. 2006-6/2, and EK-2-
136 18/2021-9). All participants gave written informed consent.

137 2.2. Exposure assessment

138 Air pollution measurements were conducted in the period from April 2010 to February 2011 and
139 methods were described in detail elsewhere (Cyrus et al., 2012; Eeftens et al., 2012b). In brief,
140 three 2-week measurements covering different seasons were averaged and adjusted for
141 temporal trends using a background monitoring site with continuous measurements. A map with
142 the locations of the measurement sites is given in Figure S2 in the online supplement. Because
143 we had not sufficient equipment to measure all 40 sites simultaneously, measurements were
144 conducted in four groups of 10 sites that were measured simultaneously. The continuous
145 monitoring location was used to adjust for differences between 14-day periods. Resulting values
146 represent annual average concentrations of the measured exposures. Nitrogen oxides (NO₂ and
147 NO_x) were measured using an Ogawa passive sampler, while PM_{2.5} and PM₁₀ were measured
148 with a Harvard impactor filter system. The PM_{coarse} fraction was calculated as the difference
149 between PM₁₀ and PM_{2.5} (Eeftens et al., 2012b). PM_{2.5} absorbance (PM_{2.5} abs) was
150 calculated from reflectance measurements of the PM_{2.5} and PM₁₀ filters and represent a

151 measure of black particles, typically representing diesel or wood burning soot. Eight *a priori*
152 selected elements of 48 measured chemical elements were analyzed in the PM fractions using
153 X-ray fluorescence (XRF) (Tsai et al., 2015). Elements were chosen to represent major
154 anthropogenic sources, based on toxicological potential, a high percentage of detected samples
155 (<75%) and a good precision of measurement (<10% coefficient of variation, except for nickel
156 (Ni) and vanadium (V) due to low concentration levels). Zinc (Zn), copper (Cu) and iron (Fe)
157 were chosen to represent non-tailpipe traffic emissions, silicon (Si) for soil material, sulfur (S) for
158 long-range transport, V and Ni for oil burning/industry and potassium (K) for biomass/wood
159 burning (de Hoogh et al., 2013; Tsai et al., 2015).

160 Land use regression (LUR) models were developed using geographic information system (GIS)
161 predictor variables from consistent European data sets, deploying data from the ESCAPE
162 project (European Study of Cohorts for Air Pollution Effects) and local data sets. GIS variables
163 included data on traffic, land use, population and household density and altitude. Based on this
164 data, study area specific LUR models were developed to estimate the concentration of air
165 pollutants at the home addresses of participants. The exact modelling procedure, including
166 description of variables and reliability assessments of results are described elsewhere (Beelen
167 et al., 2013; de Hoogh et al., 2013; Eeftens et al., 2012a). Exposure could not be modelled for
168 individuals residing above 600m altitude or closer than 300m to the state border (Beelen et al.,
169 2014). In addition to modeled exposures, traffic intensity on the nearest road (vehicles per day)
170 and total traffic load (intensity multiplied by length) on all major roads within a 100 m buffer,
171 were also analyzed (Beelen et al., 2014).

172 2.3. Statistical analysis

173 Multivariate linear regression was used to analyze associations between exposure to air
174 pollution parameters and GGT. The outcome variable GGT was normalized using the natural
175 logarithm and results are expressed as percent change in GGT. DFBETA statistics as well as
176 graphical analyses plotting leverage against squared predictors were used to test for potential
177 outliers and influential points. Three different models with increasing complexity, using pre-
178 defined covariate adjustment sets were used to analyze potential associations (Model 1:
179 calendar year of recruitment (categorical variable using cubic splines (Beelen et al., 2014), age,
180 sex; model 2 additionally adjusted for BMI (continuous), smoking status, marital status,
181 occupational status and class; model 3 (main model) further adjusted for neighborhood SES
182 (mean income, unemployment rate, urbanicity)). STATA version 14.0 was used for all statistical
183 analyses.

184

185 2.4. Sensitivity analysis

186 We calculated model 3 in data sets restricting to individuals without cancer history and with
187 stable residential history ten years before baseline, respectively. We accounted for potential
188 metabolic disorders by additional adjustments for biomarkers (total cholesterol (TC),
189 triglycerides (TG), glucose) which are also linked to GGT and liver disease and have been
190 shown to be linked to air pollution. However, we acknowledge that changes in biomarkers may
191 be either the result of confounding or they may act as intermediates. Air pollution exposure was
192 analyzed as a continuous variable. Traffic indicators were analyzed adjusting in addition for
193 background NO₂ concentrations. In addition, two-pollutant models were calculated, adjusting
194 PM and nitric oxides for other exposures and S with metals and vice versa. As different
195 pollutants may reflect the same source, acting as surrogates for each other, we restricted
196 analyses to less correlated exposures ($\rho < 0.7$) and marked exposures with ρ between 0.5 and
197 0.7. As potential effect modifiers, we examined age (cut point: 65 years), sex and smoking
198 status by including an interaction term and calculating the related effect estimates in the
199 respective strata.

200 3. RESULTS

201 3.1. *Characteristics of the study population*

202 Of the originally recruited 185,330 participants, 53,423 participants were excluded as home
203 address exposure assignment was impossible, leaving 131,907 participants. Further 15,798
204 participants were excluded because of missing values for variables included in model 3
205 (including 1,779 because of missing GGT values), amounting to a final analysis population of
206 116,109 participants (Figure S1 in the online supplement). The study population (55.9% female)
207 was characterized by a mean age of 41.9 (± 14.9) years at recruitment and slightly elevated
208 mean BMI \pm standard deviation (SD) of 24.8 \pm 4.3 (Table 1). Prevalence of smoking history was
209 30.1% with combined current and ex-smokers. Complete population characteristics are
210 presented in Table 1 and characteristics of the originally recruited population are shown in Table
211 S1 in the online supplement. The study population for this work was very similar to the original
212 population regarding demographics, potential confounders and biomarkers.

213

214 Mean \pm SD annual exposure values were 19.93 \pm 5.46 $\mu\text{g}/\text{m}^3$ for NO₂, 40.04 \pm 9.54 $\mu\text{g}/\text{m}^3$ for
215 NO_x, 13.58 \pm 1.22 $\mu\text{g}/\text{m}^3$ for PM_{2.5}, 1.66 \pm 0.22 10⁻⁵/m for PM_{2.5abs}, 20.65 \pm 2.38 $\mu\text{g}/\text{m}^3$ for
216 PM₁₀ and 6.68 \pm 0.90 $\mu\text{g}/\text{m}^3$ for PM_{coarse}. Elementary composition of PM_{2.5} and PM₁₀, as

217 well as traffic indicators are summarized in Table 2. The outcome GGT depicts a strong
218 variance among participants with a median of 12.0 U/L and an interquartile range (IQR) of 11.0
219 U/L (Table 2). Pearson correlation coefficients between different exposure variables range from
220 $\rho = -0.05$ for the correlation between PM_{2.5} (S) and PM₁₀ (V) and $\rho = 0.87$ for the correlation
221 between PM_{2.5} and PM_{2.5} (K) (Supplementary material: Table S2).

222 3.2. *Associations between air pollution and GGT*

224 Analyses of the main model showed average percentage increases of GGT concentration per
225 IQR, ranging from 0.53% (95% confidence interval (CI): 0.05%, 1.01%) per 7.44 $\mu\text{g}/\text{m}^3$ for NO₂
226 to 1.20% (95%-CI: 0.73%, 1.68%) per 1.56 $\mu\text{g}/\text{m}^3$ for PM_{2.5}. PM₁₀, PM_{2.5}abs and NO_x were
227 also positively associated with GGT concentration, but PM_{coarse} was not (Table 3). Traffic
228 indicators were also not associated with GGT levels. Results from elementary composition of
229 PM_{2.5} and PM₁₀ are presented in Table 4. Most observed associations were positive with the
230 strongest association observed for PM_{2.5} (S) with an increase of 1.40% (95%-CI: 0.85%,
231 1.95%) per IQR (45.72 ng/m³). Of the divalent metals, only Cu and Zn showed a positive
232 association. PM_{2.5} (Si) was negatively associated with an average change of GGT
233 concentration by -0.48% (95%-CI: -0.93%, -0.02%) per IQR (9.51 ng/m³), whereas PM₁₀ (Si)
234 was not.

235 3.3. *Two-pollutant models*

236 Results from two-pollutant models suggest, that associations of NO_x and PM_{2.5} were generally
237 robust to adjustment for a second pollutant, while associations observed for NO₂, PM₁₀ and
238 PM_{2.5}abs were less robust (Table 5). PM_{2.5}, PM_{2.5}abs and PM₁₀ were also adjusted for
239 elementary composition of PM_{2.5} and PM₁₀. PM_{2.5} was generally robust to adjustment with the
240 strongest observed adjustment effect for PM_{2.5} (S) changing the estimate for the increase in
241 GGT concentration from 3.90 (95%-CI: 2.35, 5.48) to 2.56 (95%-CI: 0.78, 4.36). PM_{2.5}abs and
242 PM₁₀ were less robust, partly losing statistical significance associated with markedly lower
243 estimates (Supplementary material Table S5). Results for the sulfur component were not much
244 influenced by adjustment for divalent metals (Figure 1).

245 3.4. *Further sensitivity analyses*

247 DFBETA statistics as well as graphical analyses for extreme values did not indicate any
248 influential outliers that may confound the results. Estimates were robust to additional
249 controlling for biomarkers of metabolic disease (TG, TC and glucose; model 4, N = 115,106)

250 with the strongest effect of adjustment on estimates for change in GGT concentrations observed
251 for NO₂ (Figure 2a), PM10 (Cu), PM10 (S), PM10 (Zn) (Supplementary material: Tables S3 and
252 S4; Model 4). The effect of adjustment on PM2.5 was negligible (Figure 2b). Adjustment model 3
253 was performed with the same population as used for model 4 and yielded similar results to the
254 model 3 population. Furthermore, patients with previous history of cancer (N = 15,369) were
255 excluded and effect estimates were robust (Figure 2a and 2b). Restriction to residents with
256 stable address for 10 years before measurement gave similar (PM2.5) or slightly stronger (NO₂)
257 associations (Figure 2b and 2a).

258 The p-values for the interaction terms for age and sex indicate no effect modification by age but
259 partly by sex with stronger increases in GGT-concentrations in women with 5.50% (95%-CI:
260 3.54%, 7.46%) vs. 1.80% (95%-CI: -0.37%, 3.97%) for PM2.5 and 4.86% (95%-CI: 2.65%,
261 7.07%) vs. 0.95% (95%-CI: -1.49%, 3.38%) for PM2.5abs (Supplementary material Table S6).
262 No consistent pattern was observed for results stratified by smoking status (Supplementary
263 material Table S7).

264

265 4. DISCUSSION

266 The present analyses revealed associations of exposure to particulate matter (PM2.5,
267 PM2.5abs, PM10) and nitrogen oxides with increased concentration of serum GGT in a large
268 population-based cohort in Vorarlberg, Austria. No association was found for PMcoarse. There
269 was a slight indication for stronger associations among females. Cu, Zn, K and S were the PM-
270 components that were most consistently associated with increasing serum GGT concentrations
271 and were robust to adjustment by other pollutants. In general, adjustment for metabolic
272 biomarkers did not change the associations.

273 The KORA study showed a statistically significant positive association only for PM2.5 with GGT
274 levels, using the same long term exposure assessment methods (Markevych et al., 2013). Our
275 effect estimates for PM2.5 (3.90% (95%-CI: 2.35% to 5.48%) per 5 µg/m³) were roughly
276 comparable to those in the KORA study region with an increase of 5.1% (95%-CI: 0.1% to
277 10.4%) of GGT per 2.8 µg/m³. This study is not only geographically close (approx. 150 km) but
278 also used the same exposure assessment methods. However, the estimates were markedly
279 lower in a cross sectional study from Taiwan (Zhang et al., 2019), with an average increase of
280 1.60% (95%-CI: 1.50% to 1.70%) per 10 µg/m³. In the China Multi-Ethnic Cohort, a cross-
281 sectional association of 3.67 (1.15, 6.24) for an increase of 10µg/m³ was observed for PM2.5

282 (Wang et al., 2022). This estimate attenuated moderately when adjusted further with life-style
283 variables and NO₂.

284 In Iran, PM₁₀ and PM_{2.5} as well as PM₁₀ at home addresses of pregnant women were
285 associated with higher levels of GGT in cord blood (Pejhan et al., 2019). Interestingly, another
286 study in Iran comparing individuals from a polluted and a less polluted city, found no difference
287 in serum GGT concentration, but in other oxidative toxic stress biomarkers such as superoxide
288 dismutase (SOD), malondialdehyde (MDA) and total antioxidant capacity (TAC) (Rezaei
289 Vandchali et al., 2020). All these studies are situated in contexts of higher PM_{2.5} concentrations
290 and it may be speculated that the stronger effects per unit increase at lower concentration levels
291 observed for other outcomes such as mortality and lung cancer (Hvidtfeldt et al., 2021; Strak et
292 al., 2021) may also hold for GGT. Furthermore the air pollution mix is likely to be different
293 between the Europe and the East and South-Asian studies.

294 For PM₁₀ our estimate of 1.90 (0.41, 3.41) is very similar to the estimate in the Chinese cohort
295 of 2.02 (0.40, 3.67), both for an increase of 10µg/m³ (Wang et al., 2022). The latter estimate
296 attenuated to 1.72 (-0.03, 3.49) when adjusted for numerous life-style factors and NO₂, similarly
297 to the attenuation of our estimate to 1.41 (-0.40, 3.26) in the two-pollutant model with NO₂.
298 Compared to the KORA study, our results for the increase in GGT concentration showed similar
299 to slightly weaker effects sizes for PM₁₀, PM_{2.5}abs, NO_x and NO₂. (Markevych et al., 2013).
300 However, the markedly larger study population of the VHM&PP cohort (5,892 in KORA, 116,109
301 in VHM&PP) yields higher precision, and therefore statistically significant effect estimates. In our
302 study, the associations of increase in GGT for NO_x, PM_{2.5} and PM_{2.5}abs were also robust in
303 two-pollutant models and sensitivity analyses taking into account additional covariates or stable
304 addresses. Detection of associations with pollutants are affected by measurement error in the
305 model and exposure contrast. The variation of exposure estimates within the cohort differed
306 between pollutant with the highest SDs in relation to the mean for NO₂ and NO_x. We did not find
307 a clear pattern of more robust associations for pollutants with a higher exposure contrast.
308 Higher precision of the individual exposure estimates will also favor detection of associations,
309 including two pollutant models. The leave one out crossvalidation R² for model performance is
310 actually highest for PM₁₀ and PM_{2.5} absorbance, followed by NO₂. Again, this seems not to be
311 directly reflected in the results. However, PM coarse which shows the weakest association is
312 measured with less precision as it is calculated as the difference between PM₁₀ and PM_{2.5}
313 (Eeftens et al., 2012b).

314 Our results are in line with animal experiments, where increased serum levels of GGT were
315 found in rats when exposed to diesel exhaust for up to 6 months (Reed et al., 2004) or to
316 gasoline fumes for 10 weeks along with other oxidative stress and inflammatory markers
317 (Abdrabouh, 2019). This is especially of relevance as in Vorarlberg the major contributor to air
318 pollution is (cross-border) traffic and especially diesel engines are very common. Further
319 laboratory experiments indicate a positive association between short-term (up to 14 days)
320 pulmonary exposure to NO₂ and expression of GGT-genes in rat lungs (Takahashi et al., 1997).
321 Similarly, intratracheal instilled PM₁₀ and PM_{2.5} obtained from Mexico city were associated
322 with increased GGT-levels in rat lungs after 24 and 72 hours (Snow et al., 2014).

323 The KORA study investigated two other classical biomarkers for liver damage, aspartate
324 transaminase (AST) and alanine transaminase (ALT), but found no association (Markevych et
325 al., 2013). This led to the interpretation that oxidative stress is the main mode of action, as
326 hepatotoxic effects would also lead to elevated levels of AST and ALT (Sallie et al., 1991).
327 However, other epidemiological studies (longterm (Pejhan et al., 2019; Zhang et al., 2019)(Li et
328 al., 2022) and shortterm (Kim et al., 2015)) and animal experiments (Abdrabouh, 2019) have
329 found associations of air pollution with increased levels of ALT and/or AST. This is confirmed by
330 a recent meta-analysis (Pan et al., 2023). Unfortunately, AST and ALT are not available in our
331 study, so that we cannot contribute a further insight on this matter.

332 There is some evidence from epidemiological studies showing that long-term exposure to air
333 pollution is associated with hepatic steatosis (Li et al., 2017) and the incidence of liver cirrhosis
334 (Orioli et al., 2019). Further evidence for an association between long term air pollution and liver
335 disease comes from studies in mice showing maternal exposure to PM_{2.5} triggers a non-
336 alcoholic steatohepatitis (NASH) like phenotype, characterized by hepatic steatosis,
337 inflammation, and fibrosis(Zheng et al., 2013). However, no corresponding associations for
338 prenatal and childhood exposure were observed (Garcia et al., 2021).

339 As potential bio-mechanism, inflammation in the lung may be propagated by systemic oxidative
340 stress and inflammatory responses similar to effects on cardiometabolic diseases (Brook et al.,
341 2010; Rajagopalan and Brook, 2012). For NAFLD specifically, mechanisms involving insulin
342 resistance and lipid metabolic disorder, hepatocyte steatosis, endoplasmic reticulum stress, and
343 intestinal dysbacteriosis have been proposed (Chen et al., 2021). It has been hypothesized that
344 air pollutants could partially pass via the lungs and the general circulation into the liver, where
345 some air pollutants may stimulate a local inflammatory response (Kim et al., 2014). In
346 experimental studies with murine models, exposure to particulate matter was found to induce

347 liver tissue inflammation through the activation of Kupffer cells and production of cytokines (Tan
348 et al., 2009) and reticulum stress response (Laing et al., 2010).

349 To our knowledge, we are the first to investigate the associations between long term exposure
350 to elemental composition of PM and serum GGT concentrations. We observed consistent
351 positive associations of GGT concentrations with Cu, K, S and Zn in both PM-fractions and a
352 negative association for Si in PM_{2.5}. The strongest associations were observed for S and Cu in
353 PM_{2.5} fractions and K in the PM₁₀ fraction. Toxicological studies provide only little insight into
354 the molecular mechanisms related to exposures to PM-elements (Kelly and Fussell, 2012). A
355 recent study investigated the association of exposures to PM-components with the plasma
356 metabolome and found a perturbation of the Glutathione metabolism linked to long-term
357 exposure to BC, Ni, V, Zi and Cu, whereas they found no association of K and S with any
358 metabolites (Nassan et al., 2021). It has been suggested that associations of S with various
359 outcomes including natural mortality, may be an effect of sulfate solubilized transition metals or
360 organic compounds acting as surrogates for observed associations (Kelly and Fussell, 2012).
361 Within our analysis, two-pollutant models were used to untangle potential effects and the effect
362 estimate for sulfur remained robust to adjustment for Fe, Cu, Ni and Zn.

363 In general, we cannot exclude the possibility that other, not measured substances in the air
364 pollution mix might influence our results. Persistent organic pollutants like monohydroxy-
365 polycyclic aromatic hydrocarbons (PAHs) have been associated with GGT before (Lee et al.,
366 2008) and have been associated with incomplete combustion of organic material, a process
367 observed in wood burning (Lee and Jacobs, 2009). This might explain the strong positive
368 association between PM₁₀ (K), an indicator for wood burning, and GGT concentration observed
369 in our analysis.

370 More studies need to be conducted to assess potential active substances and further
371 understand the impact of the chemical composition of air pollution on associated effects like
372 increases in biomarkers, cancer or mortality outcomes.

373 One strength of this study is the large study population (116,109), recruited from the general
374 public using standardized protocols and information on many important confounders, including
375 the measurement of metabolic factors. Modelling of air pollution was performed using a
376 standardized protocol already applied in various cohorts and assessing the exposure
377 specifically at the home address of each participant.

378 There are several limitations in this study. First, our study design does not allow a judgement on
379 causal interference. Furthermore, determination and measurement of covariates and outcome

380 precede the exposure measurement. However, in studies of long-term effects spatial contrasts
381 are most important and several studies showed that they are stable over many years (Cesaroni
382 et al., 2012; Eeftens et al., 2011; Wang et al., 2013)

383 Additionally, a potential source of confounding could be liver disease or alcohol
384 consumption/abuse. This was addressed within sensitivity analyses, excluding potential outliers
385 (GGT >600 U/L, cancer, including liver cancer cases). An analysis based directly on alcohol
386 consumption/abuse was not possible as no information about dietary patterns were available.
387 We were able to adjust for components of the metabolic syndrome, i.e., diabetes status,
388 triglycerides, total cholesterol (as a surrogate for HDL), BMI (as an approximation to central
389 obesity), and blood pressure. Unfortunately, information on other liver enzymes (ALT, AST) was
390 not available.

391 Our study contributes novelty to the field with the investigation of several air pollution
392 components from different sources, in addition to PM_{2.5}, and highlights that this understudied
393 area merits further investigation for an outcome that play a central role in disease and
394 detoxification of noxious exposures. Our novel exploration of the possible relation of sulfur and
395 metal ions in causing physiological damage especially via oxidative stress needs to be
396 investigated in future studies, ideally comprising further heavy metals (e.g. Cd and Pb) that we
397 could not investigate. In addition, we were able to adjust for relevant biomarkers that could be
398 confounding variables in the sensitivity analyses.

399 In conclusion, long-term exposure to air pollution (PM_{2.5}, PM₁₀, NO₂, NO_x) as well as certain
400 elements, representing traffic emissions, long range transport and wood burning, were positively
401 associated with baseline GGT concentration suggesting that air pollution has adverse effects on
402 liver metabolism. The observed long term air pollution within the area of Vorarlberg is relatively
403 low, with most individuals in our cohort living in locations with annual average exposures below
404 the current European limit values for PM_{2.5} (25 µg/m³) and NO₂ (40 µg/m³). This highlights the
405 necessity to further reduce ambient air pollution, in alignment with the WHO-air quality
406 guidelines from 2021, in order to protect the population from adverse health effects attributed to
407 air pollution exposure.

408

409

410

411

412 Acknowledgements: This work was supported by the European Community's Seventh
413 Framework Program (FP7/2007-2011) projects ESCAPE [211250] and TRANSPHORM
414 [243406].

415

416 The authors declare no competing financial interest

417

418 REFERENCES

- 419 Abdrabouh, A.E., 2019. Liver disorders related to exposure to gasoline fumes in male rats and
420 role of fenugreek seed supplementation. *Environ. Sci. Pollut. Res. Int.* 26, 8949–8957.
421 <https://doi.org/10.1007/s11356-019-04307-x>
- 422 Anderson, J.O., Thundiyil, J.G., Stolbach, A., 2012. Clearing the Air: A Review of the Effects of
423 Particulate Matter Air Pollution on Human Health. *J. Med. Toxicol.* 8, 166–175.
424 <https://doi.org/10.1007/s13181-011-0203-1>
- 425 Beelen, R., Hoek, G., Raaschou-Nielsen, O., Stafoggia, M., Andersen, Z.J., Weinmayr, G.,
426 Hoffmann, B., Wolf, K., Samoli, E., Fischer, P.H., Nieuwenhuijsen, M.J., Xun, W.W.,
427 Katsouyanni, K., Dimakopoulou, K., Marcon, A., Vartiainen, E., Lanki, T., Yli-Tuomi, T.,
428 Oftedal, B., Schwarze, P.E., Nafstad, P., De Faire, U., Pedersen, N.L., Östenson, C.-G.,
429 Fratiglioni, L., Penell, J., Korek, M., Pershagen, G., Eriksen, K.T., Overvad, K., Sørensen,
430 M., Eeftens, M., Peeters, P.H., Meliefste, K., Wang, M., Bueno-de-Mesquita, H.B., Sugiri,
431 D., Krämer, U., Heinrich, J., de Hoogh, K., Key, T., Peters, A., Hampel, R., Concin, H.,
432 Nagel, G., Jaensch, A., Ineichen, A., Tsai, M.-Y., Schaffner, E., Probst-Hensch, N.M.,
433 Schindler, C., Ragettli, M.S., Vilier, A., Clavel-Chapelon, F., Declercq, C., Ricceri, F.,
434 Sacerdote, C., Galassi, C., Migliore, E., Ranzi, A., Cesaroni, G., Badaloni, C., Forastiere,
435 F., Katsoulis, M., Trichopoulou, A., Keuken, M., Jedynska, A., Kooter, I.M., Kukkonen, J.,
436 Sokhi, R.S., Vineis, P., Brunekreef, B., 2015. Natural-cause mortality and long-term
437 exposure to particle components: an analysis of 19 European cohorts within the multi-
438 center ESCAPE project. *Environ. Health Perspect.* 123, 525–33.
439 <https://doi.org/10.1289/ehp.1408095>
- 440 Beelen, R., Hoek, G., Vienneau, D., Eeftens, M., Dimakopoulou, K., Pedeli, X., Tsai, M.-Y.,
441 Künzli, N., Schikowski, T., Marcon, A., Eriksen, K.T., Raaschou-Nielsen, O., Stephanou,
442 E., Patelarou, E., Lanki, T., Yli-Tuomi, T., Declercq, C., Falq, G., Stempfelet, M., Birk, M.,
443 Cyrus, J., von Klot, S., Nádor, G., Varró, M.J., Dédelé, A., Gražulevičienė, R., Mölter, A.,
444 Lindley, S., Madsen, C., Cesaroni, G., Ranzi, A., Badaloni, C., Hoffmann, B.,
445 Nonnemacher, M., Krämer, U., Kuhlbusch, T., Cirach, M., de Nazelle, A., Nieuwenhuijsen,
446 M., Bellander, T., Korek, M., Olsson, D., Strömgren, M., Dons, E., Jerrett, M., Fischer, P.,
447 Wang, M., Brunekreef, B., de Hoogh, K., 2013. Development of NO₂ and NO_x land use
448 regression models for estimating air pollution exposure in 36 study areas in Europe – The
449 ESCAPE project. *Atmos. Environ.* 72, 10–23.
450 <https://doi.org/10.1016/j.atmosenv.2013.02.037>

451 Beelen, R., Raaschou-Nielsen, O., Stafoggia, M., Andersen, Z.J., Weinmayr, G., Hoffmann, B.,
452 Wolf, K., Samoli, E., Fischer, P., Nieuwenhuijsen, M., Vineis, P., Xun, W.W., Katsouyanni,
453 K., Dimakopoulou, K., Oudin, A., Forsberg, B., Modig, L., Havulinna, A.S., Lanki, T.,
454 Turunen, A., Oftedal, B., Nystad, W., Nafstad, P., De Faire, U., Pedersen, N.L., Östenson,
455 C.-G., Fratiglioni, L., Penell, J., Korek, M., Pershagen, G., Eriksen, K.T., Overvad, K.,
456 Ellermann, T., Eeftens, M., Peeters, P.H., Meliefste, K., Wang, M., Bueno-de-Mesquita, B.,
457 Sugiri, D., Krämer, U., Heinrich, J., de Hoogh, K., Key, T., Peters, A., Hampel, R., Concin,
458 H., Nagel, G., Ineichen, A., Schaffner, E., Probst-Hensch, N., Künzli, N., Schindler, C.,
459 Schikowski, T., Adam, M., Phuleria, H., Vilier, A., Clavel-Chapelon, F., Declercq, C., Grioni,
460 S., Krogh, V., Tsai, M.-Y., Ricceri, F., Sacerdote, C., Galassi, C., Migliore, E., Ranzi, A.,
461 Cesaroni, G., Badaloni, C., Forastiere, F., Tamayo, I., Amiano, P., Dorransoro, M.,
462 Katsoulis, M., Trichopoulou, A., Brunekreef, B., Hoek, G., 2014. Effects of long-term
463 exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts
464 within the multicentre ESCAPE project. *Lancet (London, England)* 383, 785–95.
465 [https://doi.org/10.1016/S0140-6736\(13\)62158-3](https://doi.org/10.1016/S0140-6736(13)62158-3)

466 Brook, R.D., Rajagopalan, S., Pope, C.A., Brook, J.R., Bhatnagar, A., Diez-Roux, A. V, Holguin,
467 F., Hong, Y., Luepker, R. V, Mittleman, M. a, Peters, A., Siscovick, D., Smith, S.C., Whitsel,
468 L., Kaufman, J.D., 2010. Particulate matter air pollution and cardiovascular disease: An
469 update to the scientific statement from the American Heart Association. *Circulation* 121,
470 2331–78. <https://doi.org/10.1161/CIR.0b013e3181d8e1>

471 Cesaroni, G., Porta, D., Badaloni, C., Stafoggia, M., Eeftens, M., Meliefste, K., Forastiere, F.,
472 2012. Nitrogen dioxide levels estimated from land use regression models several years
473 apart and association with mortality in a large cohort study. *Environ. Health* 11, 48.
474 <https://doi.org/10.1186/1476-069X-11-48>

475 Chen, J., Hoek, G., 2020. Long-term exposure to PM and all-cause and cause-specific mortality:
476 A systematic review and meta-analysis. *Environ. Int.* 143, 105974.
477 <https://doi.org/10.1016/j.envint.2020.105974>

478 Chen, J., Wu, L., Yang, G., Zhang, C., Liu, X., Sun, X., Chen, X., Wang, N., 2021. The influence
479 of PM_{2.5} exposure on non-alcoholic fatty liver disease. *Life Sci.* 270, 119135.
480 <https://doi.org/10.1016/j.lfs.2021.119135>

481 Ciabattini, M., Rizzello, E., Lucaroni, F., Palombi, L., Boffetta, P., 2021. Systematic review and
482 meta-analysis of recent high-quality studies on exposure to particulate matter and risk of
483 lung cancer. *Environ. Res.* 196, 110440. <https://doi.org/10.1016/j.envres.2020.110440>

484 Corti, A., Belcastro, E., Dominici, S., Maellaro, E., Pompella, A., 2020. The dark side of gamma-
485 glutamyltransferase (GGT): Pathogenic effects of an 'antioxidant' enzyme. *Free Radic.*
486 *Biol. Med.* 160, 807–819. <https://doi.org/10.1016/j.freeradbiomed.2020.09.005>

487 Cyrus, J., Eeftens, M., Heinrich, J., Ampe, C., Armengaud, A., Beelen, R., Bellander, T.,
488 Beregszaszi, T., Birk, M., Cesaroni, G., Cirach, M., de Hoogh, K., De Nazelle, A., de Vocht,
489 F., Declercq, C., Dédelé, A., Dimakopoulou, K., Eriksen, K., Galassi, C., Gražulevičienė, R.,
490 Grivas, G., Gruzieva, O., Gustafsson, A.H., Hoffmann, B., Iakovides, M., Ineichen, A.,
491 Krämer, U., Lanki, T., Lozano, P., Madsen, C., Meliefste, K., Modig, L., Mölter, A., Mosler,
492 G., Nieuwenhuijsen, M., Nonnemacher, M., Oldenwening, M., Peters, A., Pontet, S.,
493 Probst-Hensch, N., Quass, U., Raaschou-Nielsen, O., Ranzi, A., Sugiri, D., Stephanou,
494 E.G., Taimisto, P., Tsai, M.-Y., Vaskövi, É., Villani, S., Wang, M., Brunekreef, B., Hoek, G.,
495 Hoogh, K., Nazelle, A., Vocht, F., Declercq, C., Dédelé, A., Dimakopoulou, K., Eriksen, K.,
496 Galassi, C., Gražulevičienė, R., Grivas, G., Gruzieva, O., Gustafsson, A.H., Hoffmann, B.,
497 Iakovides, M., Ineichen, A., Krämer, U., Lanki, T., Lozano, P., Madsen, C., Meliefste, K.,
498 Modig, L., Mölter, A., Mosler, G., Nieuwenhuijsen, M., Nonnemacher, M., Oldenwening, M.,
499 Peters, A., Pontet, S., Probst-Hensch, N., Quass, U., Raaschou-Nielsen, O., Ranzi, A.,
500 Sugiri, D., Stephanou, E.G., Taimisto, P., Tsai, M.-Y., Vaskövi, É., Villani, S., Wang, M.,
501 Brunekreef, B., Hoek, G., 2012. Variation of NO₂ and NO_x concentrations between and
502 within 36 European study areas. *Atmos. Environ.* 62, 374–390.
503 <https://doi.org/10.1016/j.atmosenv.2012.07.080>

504 de Hoogh, K., Wang, M., Adam, M., Badaloni, C., Beelen, R., Birk, M., Cesaroni, G., Cirach, M.,
505 Declercq, C., Dédelé, A., Dons, E., de Nazelle, A., Eeftens, M., Eriksen, K., Eriksson, C.,
506 Fischer, P., Gražulevičienė, R., Gryparis, A., Hoffmann, B., Jerrett, M., Katsouyanni, K.,
507 Iakovides, M., Lanki, T., Lindley, S., Madsen, C., Mölter, A., Mosler, G., Nádor, G.,
508 Nieuwenhuijsen, M., Pershagen, G., Peters, A., Phuleria, H., Probst-Hensch, N.,
509 Raaschou-Nielsen, O., Quass, U., Ranzi, A., Stephanou, E., Sugiri, D., Schwarze, P., Tsai,
510 M.-Y., Yli-Tuomi, T., Varró, M.J., Vienneau, D., Weinmayr, G., Brunekreef, B., Hoek, G.,
511 2013. Development of Land Use Regression Models for Particle Composition in Twenty
512 Study Areas in Europe. *Environ. Sci. Technol.* 47, 5778–5786.
513 <https://doi.org/10.1021/es400156t>

514 Dominici, S., Paolicchi, A., Corti, A., Maellaro, E., Pompella, A., 2005. Prooxidant Reactions
515 Promoted by Soluble and Cell-Bound γ -Glutamyltransferase Activity, in: Sies, H., Packer,
516 L. (Eds.), *Glu[Ta]Thione Transferases and Gamma-Glutamyl Transpeptidases, Methods in*

517 Enzymology, 0076-6879 TS - CrossRef. Elsevier Academic Press, Amsterdam, London,
518 pp. 484–501. [https://doi.org/https://doi.org/10.1016/S0076-6879\(05\)01029-3](https://doi.org/https://doi.org/10.1016/S0076-6879(05)01029-3)

519 Eeftens, M., Beelen, R., de Hoogh, K., Bellander, T., Cesaroni, G., Cirach, M., Declercq, C.,
520 Dédelé, A., Dons, E., de Nazelle, A., Dimakopoulou, K., Eriksen, K., Falq, G., Fischer, P.,
521 Galassi, C., Gražulevičienė, R., Heinrich, J., Hoffmann, B., Jerrett, M., Keidel, D., Korek,
522 M., Lanki, T., Lindley, S., Madsen, C., Mölter, A., Nádor, G., Nieuwenhuijsen, M.,
523 Nonnemacher, M., Pedeli, X., Raaschou-Nielsen, O., Patelarou, E., Quass, U., Ranzi, A.,
524 Schindler, C., Stempfelet, M., Stephanou, E., Sugiri, D., Tsai, M.-Y., Yli-Tuomi, T., Varró,
525 M.J., Vienneau, D., Klot, S. von, Wolf, K., Brunekreef, B., Hoek, G., 2012a. Development of
526 Land Use Regression models for PM(2.5), PM(2.5) absorbance, PM(10) and PM(coarse) in
527 20 European study areas; results of the ESCAPE project. *Environ. Sci. Technol.* 46,
528 11195–205. <https://doi.org/10.1021/es301948k>

529 Eeftens, M., Beelen, R., Fischer, P., Brunekreef, B., Meliefste, K., Hoek, G., 2011. Stability of
530 measured and modelled spatial contrasts in NO(2) over time. *Occup. Environ. Med.* 68,
531 765–70. <https://doi.org/10.1136/oem.2010.061135>

532 Eeftens, M., Tsai, M.-Y., Ampe, C., Anwander, B., Beelen, R., Bellander, T., Cesaroni, G.,
533 Cirach, M., Cyrus, J., de Hoogh, K., De Nazelle, A., de Vocht, F., Declercq, C., Dédelé, A.,
534 Eriksen, K., Galassi, C., Gražulevičienė, R., Grivas, G., Heinrich, J., Hoffmann, B.,
535 Iakovides, M., Ineichen, A., Katsouyanni, K., Korek, M., Krämer, U., Kuhlbusch, T., Lanki,
536 T., Madsen, C., Meliefste, K., Mölter, A., Mosler, G., Nieuwenhuijsen, M., Oldenwening, M.,
537 Pennanen, A., Probst-Hensch, N., Quass, U., Raaschou-Nielsen, O., Ranzi, A.,
538 Stephanou, E., Sugiri, D., Udvardy, O., Vaskövi, É., Weinmayr, G., Brunekreef, B., Hoek,
539 G., 2012b. Spatial variation of PM2.5, PM10, PM2.5 absorbance and PMcoarse
540 concentrations between and within 20 European study areas and the relationship with NO2
541 – Results of the ESCAPE project. *Atmos. Environ.* 62, 303–317.
542 <https://doi.org/10.1016/j.atmosenv.2012.08.038>

543 Garcia, E., Stratakis, N., Valvi, D., Maitre, L., Varo, N., Aasvang, G.M., Andrusaityte, S.,
544 Basagana, X., Casas, M., de Castro, M., Fossati, S., Grazuleviciene, R., Heude, B., Hoek,
545 G., Krog, N.H., McEachan, R., Nieuwenhuijsen, M., Roumeliotaki, T., Slama, R., Urquiza,
546 J., Vafeiadi, M., Vos, M.B., Wright, J., Conti, D. V., Berhane, K., Vrijheid, M., McConnell,
547 R., Chatzi, L., 2021. Prenatal and childhood exposure to air pollution and traffic and the risk
548 of liver injury in European children. *Environ. Epidemiol.* 5, e153.
549 <https://doi.org/10.1097/EE9.0000000000000153>

550 Hamra, G.B., Laden, F., Cohen, A.J., Raaschou-Nielsen, O., Brauer, M., Loomis, D., 2015.
551 Lung Cancer and Exposure to Nitrogen Dioxide and Traffic: A Systematic Review and
552 Meta-Analysis. *Environ. Health Perspect.* 123, 1107–12.
553 <https://doi.org/10.1289/ehp.1408882>

554 Huangfu, P., Atkinson, R., 2020. Long-term exposure to NO₂ and O₃ and all-cause and
555 respiratory mortality: A systematic review and meta-analysis. *Environ. Int.* 144, 105998.
556 <https://doi.org/10.1016/j.envint.2020.105998>

557 Hvidtfeldt, U.A., Severi, G., Andersen, Z.J., Atkinson, R., Bauwelinck, M., Bellander, T.,
558 Boutron-Ruault, M.-C., Brandt, J., Brunekreef, B., Cesaroni, G., Chen, J., Concin, H.,
559 Forastiere, F., van Gils, C.H., Gulliver, J., Hertel, O., Hoek, G., Hoffmann, B., de Hoogh, K.,
560 Janssen, N., Jöckel, K.-H., Jørgensen, J.T., Katsouyanni, K., Ketzel, M., Klompmaker,
561 J.O., Krog, N.H., Lang, A., Leander, K., Liu, S., Ljungman, P.L.S., Magnusson, P.K.E.,
562 Mehta, A.J., Nagel, G., Oftedal, B., Pershagen, G., Peter, R.S., Peters, A., Renzi, M.,
563 Rizzuto, D., Rodopoulou, S., Samoli, E., Schwarze, P.E., Sigsgaard, T., Simonsen, M.K.,
564 Stafoggia, M., Strak, M., Vienneau, D., Weinmayr, G., Wolf, K., Raaschou-Nielsen, O.,
565 Fecht, D., 2021. Long-term low-level ambient air pollution exposure and risk of lung cancer
566 – A pooled analysis of 7 European cohorts. *Environ. Int.* 146, 106249.
567 <https://doi.org/10.1016/j.envint.2020.106249>

568 Kelly, F.J., Fussell, J.C., 2012. Size, source and chemical composition as determinants of
569 toxicity attributable to ambient particulate matter. *Atmos. Environ.* 60, 504–526.
570 <https://doi.org/10.1016/j.atmosenv.2012.06.039>

571 Kim, J.W., Park, S., Lim, C.W., Lee, K., Kim, B., 2014. The Role of Air Pollutants in Initiating
572 Liver Disease. *Toxicol. Res.* 30, 65–70. <https://doi.org/10.5487/TR.2014.30.2.065>

573 Kim, K.-N., Lee, H., Kim, J.H., Jung, K., Lim, Y.-H., Hong, Y.-C., 2015. Physical Activity- and
574 Alcohol-dependent Association Between Air Pollution Exposure and Elevated Liver
575 Enzyme Levels: An Elderly Panel Study. *J. Prev. Med. Public Health* 48, 151–69.
576 <https://doi.org/10.3961/jpmp.15.014>

577 Koceva, M.M., Brandmüller, T., Lupu, I., Önnersfors, Å., Corselli-Nordblad, L., Coyette, C.,
578 Johansson, A., Strandell, H., Wolff, P. (Eds.), 2016. *Urban Europe, 2016* editi. ed,
579 *Statistical books / Eurostat. Publications Office of the European Union, Luxembourg.*

580 Koenig, G., Seneff, S., 2015. Gamma-Glutamyltransferase: A Predictive Biomarker of Cellular
581 Antioxidant Inadequacy and Disease Risk. *Dis. Markers* 2015, 1–18.

582 <https://doi.org/10.1155/2015/818570>

583 Laing, S., Wang, G., Briazova, T., Zhang, C., Wang, A., Zheng, Z., Gow, A., Chen, A.F.,
584 Rajagopalan, S., Chen, L.C., Sun, Q., Zhang, K., 2010. Airborne particulate matter
585 selectively activates endoplasmic reticulum stress response in the lung and liver tissues.
586 *Am. J. Physiol. Physiol.* 299, C736–C749. <https://doi.org/10.1152/ajpcell.00529.2009>

587 Lee, D.-H., Jacobs, D.R., 2009. Is serum γ -glutamyltransferase an exposure marker of
588 xenobiotics? Empirical evidence with polycyclic aromatic hydrocarbon. *Clin. Chem. Lab.*
589 *Med.* 47, 860–862. <https://doi.org/10.1515/CCLM.2009.197>

590 Lee, D.-H., Steffes, M.W., Jacobs, D.R., 2008. Can persistent organic pollutants explain the
591 association between serum γ -glutamyltransferase and type 2 diabetes? *Diabetologia* 51,
592 402–407. <https://doi.org/10.1007/s00125-007-0896-5>

593 Li, W., Dorans, K.S., Wilker, E.H., Rice, M.B., Long, M.T., Schwartz, J., Coull, B.A., Koutrakis,
594 P., Gold, D.R., Fox, C.S., Mittleman, M.A., 2017. Residential Proximity to Major Roadways,
595 Fine Particulate Matter, and Hepatic Steatosis. *Am. J. Epidemiol.* 186, 857–865.
596 <https://doi.org/10.1093/aje/kwx127>

597 Li, Y., Yuan, X., Wei, J., Sun, Y., Ni, W., Zhang, H., Zhang, Y., Wang, R., Xu, R., Liu, T., Yang,
598 C., Chen, G., Xu, J., Liu, Y., 2022. Long-term exposure to ambient air pollution and serum
599 liver enzymes in older adults: A population-based longitudinal study. *Ann. Epidemiol.* 74,
600 1–7. <https://doi.org/10.1016/j.annepidem.2022.05.011>

601 Lim, J.-S., Yang, J.-H., Chun, B.-Y., Kam, S., Jacobs, D.R., Lee, D.-H., 2004. Is serum γ -
602 glutamyltransferase inversely associated with serum antioxidants as a marker of oxidative
603 stress? *Free Radic. Biol. Med.* 37, 1018–1023.
604 <https://doi.org/10.1016/j.freeradbiomed.2004.06.032>

605 Liu, Q., Xu, C., Ji, G., Liu, H., Shao, W., Zhang, C., Gu, A., Zhao, P., 2017. Effect of exposure to
606 ambient PM_{2.5} pollution on the risk of respiratory tract diseases: a meta-analysis of cohort
607 studies. *J. Biomed. Res.* 31, 130–142. <https://doi.org/10.7555/JBR.31.20160071>

608 Maciejczyk, P., Chen, L.-C., Thurston, G., 2021. The Role of Fossil Fuel Combustion Metals in
609 PM_{2.5} Air Pollution Health Associations. *Atmosphere (Basel)*. 12, 1086.
610 <https://doi.org/10.3390/atmos12091086>

611 Markevych, I., Wolf, K., Hampel, R., Breitner, S., Schneider, A., von Klot, S., Cyrus, J., Heinrich,
612 J., Döring, A., Beelen, R., Koenig, W., Peters, A., 2013. Air Pollution and Liver Enzymes.
613 *Epidemiology* 24, 934–935. <https://doi.org/10.1097/EDE.0b013e3182a77600>

614 Mills, N.L., Donaldson, K., Hadoke, P.W., Boon, N. a, MacNee, W., Cassee, F.R., Sandström,
615 T., Blomberg, A., Newby, D.E., 2009. Adverse cardiovascular effects of air pollution. *Nat.*
616 *Clin. Pract. Cardiovasc. Med.* 6, 36–44. <https://doi.org/10.1038/ncpcardio1399>

617 Morris, G., Anderson, G., Dean, O., Berk, M., Galecki, P., Martin-Subero, M., Maes, M., 2014.
618 The glutathione system. *Mol. Neurobiol.* 50, 1059–1084. [https://doi.org/10.1007/s12035-](https://doi.org/10.1007/s12035-014-8705-x)
619 014-8705-x

620 Nassan, F.L., Wang, C., Kelly, R.S., Lasky-Su, J.A., Vokonas, P.S., Koutrakis, P., Schwartz,
621 J.D., 2021. Ambient PM_{2.5} species and ultrafine particle exposure and their differential
622 metabolomic signatures. *Environ. Int.* 151, 106447.
623 <https://doi.org/10.1016/j.envint.2021.106447>

624 Orioli, R., Antonucci, C., Scortichini, M., Cerza, F., Marando, F., Ancona, C., Manes, F., Davoli,
625 M., Michelozzi, P., Forastiere, F., Cesaroni, G., 2019. Exposure to Residential Greenness
626 as a Predictor of Cause-Specific Mortality and Stroke Incidence in the Rome Longitudinal
627 Study. *Environ. Health Perspect.* 127, 027002. <https://doi.org/10.1289/EHP2854>

628 Pan, L., Sui, J., Xu, Y., Zhao, Q., Cai, Y., Sun, G., Xia, H., 2023. Effect of Fine Particulate
629 Matter Exposure on Liver Enzymes: A Systematic Review and Meta-Analysis. *Int. J.*
630 *Environ. Res. Public Health* 20, 2803. <https://doi.org/10.3390/ijerph20042803>

631 Paolicchi, A., Dominici, S., Pieri, L., Maellaro, E., Pompella, A., 2002. Glutathione catabolism as
632 a signaling mechanism. *Biochem. Pharmacol.* 64, 1027–1035.
633 [https://doi.org/10.1016/S0006-2952\(02\)01173-5](https://doi.org/10.1016/S0006-2952(02)01173-5)

634 Pejhan, A., Agah, J., Adli, A., Mehrabadi, S., Raoufinia, R., Mokamel, A., Abroudi, M.,
635 Ghalenovi, M., Sadeghi, Z., Bolghanabadi, Z., Bazghandi, M.S., Hamidnia, M., Salimi, F.,
636 Pajohanfar, N.S., Dadvand, P., Rad, A., Miri, M., 2019. Exposure to air pollution during
637 pregnancy and newborn liver function. *Chemosphere* 226, 447–453.
638 <https://doi.org/10.1016/j.chemosphere.2019.03.185>

639 Rajagopalan, S., Brook, R.D., 2012. Air pollution and type 2 diabetes: mechanistic insights.
640 *Diabetes* 61, 3037–45. <https://doi.org/10.2337/db12-0190>

641 Reed, M.D., Gigliotti, A.P., McDonald, J.D., Seagrave, J.C., Seilkop, S.K., Mauderly, J.L., 2004.
642 Health effects of subchronic exposure to environmental levels of diesel exhaust. *Inhal.*
643 *Toxicol.* 16, 177–93. <https://doi.org/10.1080/08958370490277146>

644 Rezaei Vandchali, N., Koolivand, A., Ranjbar, A., Zarei, P., Fathi, M., Malekafzali, S.,
645 Mollamohammadi, N., Jalali-Mashayekhi, F., 2020. Oxidative toxic stress and p53 level in

646 healthy subjects occupationally exposed to outdoor air Pollution - a cross-sectional study in
647 Iran. *Ann. Agric. Environ. Med.* 27, 585–590. <https://doi.org/10.26444/aaem/126313>

648 Ruttman, E., Brant, L.J., Concin, H., Diem, G., Rapp, K., Ulmer, H., 2005. γ -
649 Glutamyltransferase as a Risk Factor for Cardiovascular Disease Mortality. *Circulation* 112,
650 2130–2137. <https://doi.org/10.1161/CIRCULATIONAHA.105.552547>

651 Sallie, R., Michael Tredger, J., Williams, R., 1991. Drugs and the liver part 1: Testing liver
652 function. *Biopharm. Drug Dispos.* 12, 251–259. <https://doi.org/10.1002/bdd.2510120403>

653 Snow, S.J., De Vizcaya-Ruiz, A., Osornio-Vargas, A., Thomas, R.F., Schladweiler, M.C.,
654 McGee, J., Kodavanti, U.P., 2014. The effect of composition, size, and solubility on acute
655 pulmonary injury in rats following exposure to Mexico city ambient particulate matter
656 samples. *J. Toxicol. Environ. Health. A* 77, 1164–82.
657 <https://doi.org/10.1080/15287394.2014.917445>

658 Strak, M., Weinmayr, G., Rodopoulou, S., Chen, J., de Hoogh, K., Andersen, Z.J., Atkinson, R.,
659 Bauwelinck, M., Bekkevold, T., Bellander, T., Boutron-Ruault, M.-C., Brandt, J., Cesaroni,
660 G., Concin, H., Fehcht, D., Forastiere, F., Gulliver, J., Hertel, O., Hoffmann, B., Hvidtfeldt,
661 U.A., Janssen, N.A.H., Jöckel, K.-H., Jørgensen, J.T., Ketzel, M., Klompaker, J.O.,
662 Lager, A., Leander, K., Liu, S., Ljungman, P., Magnusson, P.K.E., Mehta, A.J., Nagel, G.,
663 Oftedal, B., Pershagen, G., Peters, A., Raaschou-Nielsen, O., Renzi, M., Rizzuto, D., van
664 der Schouw, Y.T., Schramm, S., Severi, G., Sigsgaard, T., Sørensen, M., Stafoggia, M.,
665 Tjønneland, A., Verschuren, W.M.M., Vienneau, D., Wolf, K., Katsouyanni, K., Brunekreef,
666 B., Hoek, G., Samoli, E., 2021. Long term exposure to low level air pollution and mortality
667 in eight European cohorts within the ELAPSE project: pooled analysis. *BMJ* n1904.
668 <https://doi.org/10.1136/bmj.n1904>

669 Takahashi, Y., Oakes, S.M., Williams, M.C., Takahashi, S., Miura, T., Joyce-Brady, M., 1997.
670 Nitrogen Dioxide Exposure Activates γ -Glutamyl Transferase Gene Expression in Rat
671 Lung. *Toxicol. Appl. Pharmacol.* 143, 388–396. <https://doi.org/10.1006/taap.1996.8087>

672 Tan, H.-H., Fiel, M.I., Sun, Q., Guo, J., Gordon, R.E., Chen, L.-C., Friedman, S.L., Odin, J.A.,
673 Allina, J., 2009. Kupffer cell activation by ambient air particulate matter exposure may
674 exacerbate non-alcoholic fatty liver disease. *J. Immunotoxicol.* 00, 090924084432057–10.
675 <https://doi.org/10.1080/15476910903241704>

676 Teschke, R., Brand, A., Strohmeyer, G., 1977. Induction of hepatic microsomal gamma-
677 glutamyltransferase activity following chronic alcohol consumption. *Biochem. Biophys. Res.*

678 Commun. 75, 718–724. [https://doi.org/10.1016/0006-291X\(77\)91531](https://doi.org/10.1016/0006-291X(77)91531)

679 Tsai, M.-Y., Hoek, G., Eeftens, M., de Hoogh, K., Beelen, R., Beregszászi, T., Cesaroni, G.,
680 Cirach, M., Cyrys, J., De Nazelle, A., de Vocht, F., Ducret-Stich, R., Eriksen, K., Galassi,
681 C., Gražuleviciene, R., Gražulevicius, T., Grivas, G., Gryparis, A., Heinrich, J., Hoffmann,
682 B., Iakovides, M., Keuken, M., Krämer, U., Künzli, N., Lanki, T., Madsen, C., Meliefste, K.,
683 Merritt, A.-S., Mölter, A., Mosler, G., Nieuwenhuijsen, M.J., Pershagen, G., Phuleria, H.,
684 Quass, U., Ranzi, A., Schaffner, E., Sokhi, R., Stempfelet, M., Stephanou, E., Sugiri, D.,
685 Taimisto, P., Tewis, M., Udvardy, O., Wang, M., Brunekreef, B., 2015. Spatial variation of
686 PM elemental composition between and within 20 European study areas — Results of the
687 ESCAPE project. *Environ. Int.* 84, 181–192. <https://doi.org/10.1016/j.envint.2015.04.015>

688 Ulmer, H., Kelleher, C.C., Fitz-Simon, N., Diem, G., Concin, H., 2007. Secular trends in
689 cardiovascular risk factors: an age-period cohort analysis of 6 98 954 health examinations
690 in 1 81 350 Austrian men and women. *J. Intern. Med.* 261, 566–576.
691 <https://doi.org/10.1111/j.1365-2796.2007.01779.x>

692 van Hoek, B., 2004. Non-alcoholic fatty liver disease: a brief review. *Scand. J. Gastroenterol.*
693 Suppl. 56–9. <https://doi.org/10.1080/00855920410011013>

694 Wang, R., Henderson, S.B., Sbihi, H., Allen, R.W., Brauer, M., 2013. Temporal stability of land
695 use regression models for traffic-related air pollution. *Atmos. Environ.* 64, 312–319.
696 <https://doi.org/10.1016/j.atmosenv.2012.09.056>

697 Wang, X., Guo, B., Yang, X., Li, J., Baima, Y., Yin, J., Yu, J., Xu, H., Zeng, C., Feng, S., Wei, J.,
698 Hong, F., Zhao, X., 2022. Role of Liver Enzymes in the Relationship Between Particulate
699 Matter Exposure and Diabetes Risk: A Longitudinal Cohort Study. *J. Clin. Endocrinol.*
700 *Metab.* 107, e4086–e4097. <https://doi.org/10.1210/clinem/dgac438>

701 Weinmayr, G., Hennig, F., Fuks, K., Nonnemacher, M., Jakobs, H., Möhlenkamp, S., Erbel, R.,
702 Jöckel, K.-H., Hoffmann, B., Moebus, S., Heinz Nixdorf Recall Investigator Group, 2015.
703 Long-term exposure to fine particulate matter and incidence of type 2 diabetes mellitus in a
704 cohort study: effects of total and traffic-specific air pollution. *Environ. Health* 14, 53.
705 <https://doi.org/10.1186/s12940-015-0031-x>

706 Whitfield, J.B., 2001. Gamma Glutamyl Transferase. *Crit. Rev. Clin. Lab. Sci.* 38, 263–355.
707 <https://doi.org/10.1080/20014091084227>

708 Yang, B.-Y., Qian, Z., Howard, S.W., Vaughn, M.G., Fan, S.-J., Liu, K.-K., Dong, G.-H., 2018.
709 Global association between ambient air pollution and blood pressure: A systematic review

710 and meta-analysis. *Environ. Pollut.* 235, 576–588.
711 <https://doi.org/10.1016/j.envpol.2018.01.001>

712 Yang, M., Cheng, H., Shen, C., Liu, J., Zhang, H., Cao, J., Ding, R., 2020. Effects of long-term
713 exposure to air pollution on the incidence of type 2 diabetes mellitus: a meta-analysis of
714 cohort studies. *Environ. Sci. Pollut. Res.* 27, 798–811. [https://doi.org/10.1007/s11356-019-](https://doi.org/10.1007/s11356-019-06824-1)
715 [06824-1](https://doi.org/10.1007/s11356-019-06824-1)

716 Yi, W., Ji, Y., Gao, H., Pan, R., Wei, Q., Cheng, J., Song, J., He, Y., Tang, C., Liu, X., Song, S.,
717 Su, H., 2021. Does the gut microbiome partially mediate the impact of air pollutants
718 exposure on liver function? Evidence based on schizophrenia patients. *Environ. Pollut.*
719 291, 118135. <https://doi.org/10.1016/j.envpol.2021.118135>

720 Yuan, C.-S., Lai, C.-S., Tseng, Y.-L., Hsu, P.-C., Lin, C.-M., Cheng, F.-J., 2021. Repeated
721 exposure to fine particulate matter constituents lead to liver inflammation and proliferative
722 response in mice. *Ecotoxicol. Environ. Saf.* 224, 112636.
723 <https://doi.org/10.1016/j.ecoenv.2021.112636>

724 Zhang, Z., Guo, C., Chang, L.-Y., Bo, Y., Lin, C., Tam, T., Hoek, G., Wong, M.C., Chan, T.-C.,
725 Lau, A.K., Lao, X.Q., 2019. Long-term exposure to ambient fine particulate matter and liver
726 enzymes in adults: a cross-sectional study in Taiwan. *Occup. Environ. Med.* 76, 488–494.
727 <https://doi.org/10.1136/oemed-2019-105695>

728 Zheng, Z., Xu, X., Zhang, X., Wang, A., Zhang, C., Hüttemann, M., Grossman, L.I., Chen, L.C.,
729 Rajagopalan, S., Sun, Q., Zhang, K., 2013. Exposure to ambient particulate matter induces
730 a NASH-like phenotype and impairs hepatic glucose metabolism in an animal model. *J.*
731 *Hepatol.* 58, 148–154. <https://doi.org/10.1016/j.jhep.2012.08.009>

732

733

734

Change in Gamma-Glutamyl-Transferase related to ambient air pollution:
robustness of results for an increase of 5 $\mu\text{g}/\text{m}^3$ in PM2.5 and of 10 $\mu\text{g}/\text{m}^3$ in NO₂

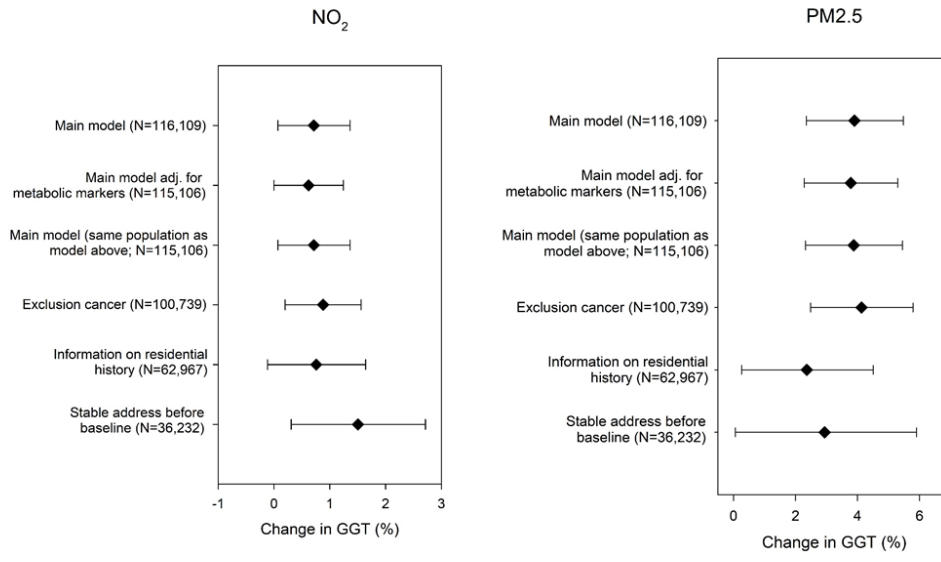


TABLE 1: Descriptive statistics of categorical and continuous variables. ^a

Variables	n (%) or Mean ± SD
Age (years), mean ± SD	41.9 ± 14.9
Female sex, n (%)	64,857 (55.9)
BMI (kg/m ²), mean ± SD	24.77 ± 4.27
Smoking status	
non-smoker	81,138 (69.9)
current smoker	27,838 (24.0)
ex-smoker	7,133 (6.1)
Marital status:	
single	19,951 (17.2)
married/ living with partner	79,387 (68.4)
divorced/ separated	8,813 (7.6)
widowed	7,958 (6.9)
Occupation:	
white collar	65,394 (56.3)
blue collar	40,326 (34.7)
others	10,389 (8.9)
Occupational status:	
employed ^b	80,794 (69.6)
unemployed	4,070 (3.5)
retired	31,245 (26.9)
Prevalent hypertension ^{a,b}	42,418 (37.0)
Glucose ^b (mg/dl)	103.0 ± 36.6
Triglycerides ^b (mg/dl)	131.8 ± 100.8
Cholesterol ^b (mg/dl)	215.6 ± 46.8
Area indicator:	
urban (small cities)	113,083 (97.4)
rural	3,026 (2.6)
Ø unemployment (%), mean ± SD	1.1 ± 0.5
mean income (EURO)	25121 ± 1273

SD = standard deviation, n = number, BMI = body mass index. Population is the same study population used for models 1-3 (n=116,109). ^a systolic blood pressure ≥140 or diastolic blood pressure ≥ 90 at baseline examination. ^b presented for participants included in model 5 (n=114,578).

TABLE 2: Descriptive statistics of air pollution parameters and serum GGT concentrations.

Exposure	Mean \pm SD	Median	Q1	Q3	IQR
NO ₂ ($\mu\text{g}/\text{m}^3$)	19.93 \pm 5.46	20.05	16.16	23.60	7.44
NO _x ($\mu\text{g}/\text{m}^3$)	40.04 \pm 9.54	39.21	33.52	45.26	11.74
PM2.5 ($\mu\text{g}/\text{m}^3$)	13.58 \pm 1.22	13.72	12.87	14.43	1.56
PM2.5 abs ^a ($10^{-5}/\text{m}$)	1.66 \pm 0.22	1.68	1.52	1.80	0.28
PM10 ($\mu\text{g}/\text{m}^3$)	20.65 \pm 2.38	20.86	19.20	22.30	3.10
PMcoarse ($\mu\text{g}/\text{m}^3$)	6.68 \pm 0.90	6.78	6.01	7.30	1.28
PM2.5 Cu (ng/m^3)	3.98 \pm 1.09	4.29	3.46	4.73	1.27
PM2.5 Fe (ng/m^3)	66.34 \pm 7.86	68.05	62.32	69.79	7.47
PM2.5 K (ng/m^3)	331.37 \pm 31.21	333.20	311.74	353.26	41.52
PM2.5 Ni (ng/m^3)	0.14 \pm 0.07	0.17	0.09	0.20	0.11
PM2.5 S (ng/m^3)	618.72 \pm 31.38	620.52	596.49	642.21	45.72
PM2.5 Si (ng/m^3)	64.15 \pm 7.08	65.26	59.98	69.49	9.51
PM2.5 Zn (ng/m^3)	22.27 \pm 3.30	22.64	19.90	24.80	4.90
PM10 Cu (ng/m^3)	8.98 \pm 2.63	9.18	7.60	10.40	2.80
PM10 Fe (ng/m^3)	319.49 \pm 44.06	328.52	296.13	338.36	42.23
PM10 K (ng/m^3)	398.17 \pm 34.93	401.23	374.84	423.36	48.52
PM10 Ni (ng/m^3)	0.20 \pm 0.18	0.21	0	0.28	0.28
PM10 S (ng/m^3)	658.60 \pm 46.38	663.21	631.44	689.99	58.55
PM10 Si (ng/m^3)	379.58 \pm 59.46	395.55	328.89	424.42	95.53
PM10 V (ng/m^3)	0.55 \pm 0.12	0.62	0.51	0.63	0.12
PM10 Zn (ng/m^3)	29.25 \pm 5.54	30.18	26.18	33.20	7.02
Traffic intensity ^b	1693 \pm 3609	500	500	500	8492 ^c
Traffic load ^d buffer (motor vehicles* km/day)	297 \pm 999	0	0	0	2350 ^c
GGT (U/L)	19.0 \pm 27.7	12	9	20	11

SD = standard deviation, Q₁ = first quartile, Q₃ = third quartile, IQR = interquartile range, ^a PM2.5 abs = PM2.5 absorbance, ^b Traffic intensity on nearest road (motor vehicles/day), ^c 5-95% range, ^d Traffic load on major roads within 100 m buffer (motor vehicles* km/day); . PM2.5 V was not available because of poor performance of the LUR-model(de Hoogh et al., 2013)

TABLE 3: Associations between serum GGT concentrations and main pollutants/traffic indicators.

Exposure (increment)	Change in GGT (95% confidence interval) ^a			
	Model 1 per fixed increment	Model 2 per fixed increment	Model 3 per fixed increment	Model 3 per IQR
NO ₂ (10 µg/m ³)	1.28 (0.63, 1.93)	0.81 (0.17, 1.46)	0.71 (0.07, 1.36)	0.53 (0.05, 1.01)
NO _x (20 µg /m ³)	3.24 (2.48, 4.00)	1.73 (0.99, 2.47)	1.57 (0.83, 2.32)	0.92 (0.48, 1.36)
PM2.5 (5 µg /m ³)	5.19 (3.68, 6.71)	4.23 (2.74, 5.74)	3.90 (2.35, 5.48)	1.20 (0.73, 1.68)
PM2.5 abs ^b (10 ⁻⁵ /m ³)	4.44 (2.77, 6.13)	3.64 (1.98, 5.34)	3.09 (1.36, 4.84)	0.86 (0.38, 1.33)
PM10 (10 µg /m ³)	3.29 (1.77, 4.83)	2.09 (0.60, 3.61)	1.90 (0.41, 3.41)	0.58 (0.13, 1.05)
PMcoarse (5 µg /m ³)	1.20 (-0.77, 3.20)	0.75 (-1.17, 2.70)	0.59 (-1.33, 2.55)	0.15 (-0.34,0.65)
Traffic intensity (5*10 ³ veh/day) ^c	0.37 (-0.12, 0.86)	-0.15 (-0.63, 0.32)	-0.16 (-0.63, 0.32)	-0.23 (-1.03, 0.58) ^d
Traffic load (4*10 ⁶ veh*m/day) ^e	1.18 (-0.25, 2.63)	0.06 (-1.31, 1.46)	0.02 (-1.36, 1.41)	0.04 (-0.77, 0.84) ^d

IQR = interquartile range; veh: motor vehicles; ^a Change is given as percentage. ^b PM2.5abs = PM2.5 absorbance; ^c Traffic intensity on nearest road (motor vehicles/day); ^d estimates with 5-95% range as increment instead of IQR; ^e Traffic load on major roads within 100 m buffer (motor vehicles* km/day) Model 1 was adjusted for calendar year of recruitment, age and sex; model 2 was additionally adjusted for BMI, smoking status, occupation and occupational and marital status; Model 3 was further adjusted for neighborhood income and unemployment rate. Traffic indicators are additionally adjusted for urban background of NO₂. statistically significant results are marked in bold.

TABLE 4: Associations between serum GGT concentration and exposure to elemental composition of PM.

Exposure (increment)	Change in GGT (95% confidence interval) ^a			
	Model 1 ^b per inc	Model 2 ^b per inc	Model 3 ^b per inc	Model 3 ^c per IQR
PM2.5 Cu (5 ng/m ³)	4.27 (2.59, 5.97)	3.99 (2.30, 5.70)	3.36 (1.52, 5.25)	0.84 (0.38, 1.31)
PM2.5 Fe (100 ng/m ³)	5.54 (0.90, 10.39)	2.68 (-1.78, 7.34)	2.07 (-2.38, 6.73)	0.15 (-0.18, 0.49)
PM2.5 K (50 ng/m ³)	0.99 (0.42, 1.56)	0.84 (0.28, 1.40)	0.71 (0.14, 1.28)	0.59 (0.12, 1.07)
PM2.5 Ni (1 ng/m ³)	4.10 (-1.07, 9.55)	3.66 (-1.42, 9.00)	2.82 (-2.24, 8.14)	0.31 (-0.25, 0.86)
PM2.5 S (200 ng/m ³)	9.50 (7.07, 11.99)	6.77 (4.43, 9.17)	6.27 (3.77, 8.82)	1.40 (0.85, 1.95)
PM2.5 Si (100 ng/m ³)	-2.54 (-7.27, 2.43)	-4.93 (-9.42, -0.21)	-4.89 (-9.39, -0.17)	-0.48 (-0.93, -0.02)
PM2.5 Zn (10 ng/m ³)	1.33 (0.25, 2.42)	1.38 (0.32, 2.45)	1.27 (0.21, 2.35)	0.62 (0.10, 1.14)
PM10 Cu (20 ng/m ³)	7.04 (4.21, 9.95)	5.19 (2.40, 8.05)	3.90 (0.88, 7.01)	0.54 (0.12, 0.95)
PM10 Fe (500 ng/m ³)	5.56 (1.41, 9.87)	1.93 (-2.02, 6.04)	1.34 (-2.60, 5.44)	0.11 (-0.22, 0.45)
PM10 K (100 ng/m ³)	3.09 (2.06, 4.14)	2.70 (1.68, 3.72)	2.54 (1.51, 3.57)	1.22 (0.73, 1.72)
PM10 Ni (2 ng/m ³)	0.17 (-3.70, 4.20)	-2.38 (-6.06, 1.44)	-2.16 (-5.85, 1.67)	-0.31 (-0.84, 0.23)
PM10 S (200 ng/m ³)	3.55 (1.99, 5.14)	2.72 (1.17, 4.29)	2.04 (0.39, 3.71)	0.59 (0.12, 1.07)
PM10 Si (500 ng/m ³)	0.70 (-2.24, 3.73)	0.85 (-2.01, 3.80)	0.83 (-2.07, 3.82)	0.16 (-0.40, 0.72)
PM10 V (3 ng/m ³)	-4.58 (-12.63, 4.22)	-5.03 (-12.84, 3.47)	-5.46 (-13.25, 3.03)	-0.22 (-0.57, 0.12)
PM10 Zn (20 ng/m ³)	1.73 (0.44, 3.03)	1.70 (0.42, 3.00)	1.32 (0.01, 2.64)	0.46 (0.00, 0.92)

^a Change in GGT with corresponding 95% CIs. ^b inc: increment; ^c model 3 presented with IQR (Table 2) as increment; Model 1 was adjusted for calendar year of recruitment, age and sex; model 2 was additionally adjusted for BMI, smoking status, occupation and occupational and marital status; Model 3 was further adjusted for neighborhood income and unemployment rate. statistically significant results are marked in bold.

TABLE 5: Results from two-pollutant models ^a for adjusted association between air pollution and GGT concentrations: Change in GGT with corresponding 95% CIs. ^b

	Exposures (increments)					
	NO ₂ (10 µg/m ³)	NO _x (20 µg /m ³)	PM2.5 (5 µg /m ³)	PM2.5 abs (10 ⁻⁵ /m ³)	PM10 (10 µg /m ³)	PMcoarse (5 µg /m ³)
	0.71 (0.07,1.36)	1.57 (0.83, 2.32)	3.90 (2.35, 5.48)	3.09 (1.36, 4.84)	1.90 (0.41, 3.41)	0.59 (-1.33, 2.55)
adjusted for						
NO ₂	NA	1.52 (0.68, 2.37)	3.90 (2.18, 5.66)	3.26 (0.95, 5.61)	1.41 (-0.40, 3.26)	NA
NO _x	0.09 (-0.63, 0.82)	NA	3.06 (1.34, 4.80)	1.75 (-0.19, 3.72)	0.82 (-0.77, 2.44)	-1.84 (-3.99, 0.36)
PM2.5	0.00 (-0.71, 0.72)	0.92 (0.09, 1.75)	NA	NA	-1.23 (-3.20, 0.78)	-1.06 (-3.05, 0.97)
PM2.5 abs	-0.09 (-0.95, 0.76)	1.21 (0.36, 2.06)	NA	NA	NA	-3.05 (-5.53, 0.51)
PM10	0.36 (-0.42, 1.15)	1.41 (0.61, 2.22)	4.80 (2.67, 6.98)	NA	NA	-1.14 (-3.42, 1.19)
PMcoarse	NA	1.93 (1.07, 2.79)	4.18 (2.54, 5.85)	4.97 (2.62, 7.38)	2.40 (0.59, 4.24)	NA

^a Model 3 was adjusted for calendar year of recruitment, age, sex, BMI, smoking status, occupation, occupational and marital status and neighborhood income and unemployment rate. ^b Results are only presented if Pearson correlation coefficients (Supplementary material: Table 2) are <0.7 and are otherwise referred to as NA. ^c PM2.5 abs = PM2.5 absorbance; statistically significant results are marked in bold.

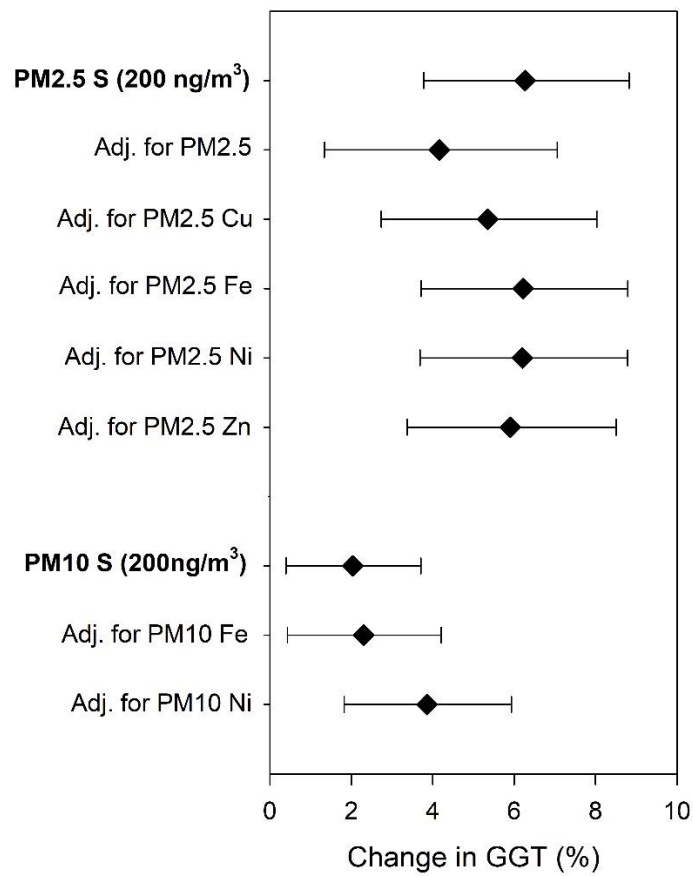


Figure 1: Two-pollutant models. PM2.5 S and PM10 S were adjusted for measured metals.

Results are only presented if Pearson correlation coefficient $p < 0.7$. 200 ng/m³ was used as an increment to calculate final estimates.

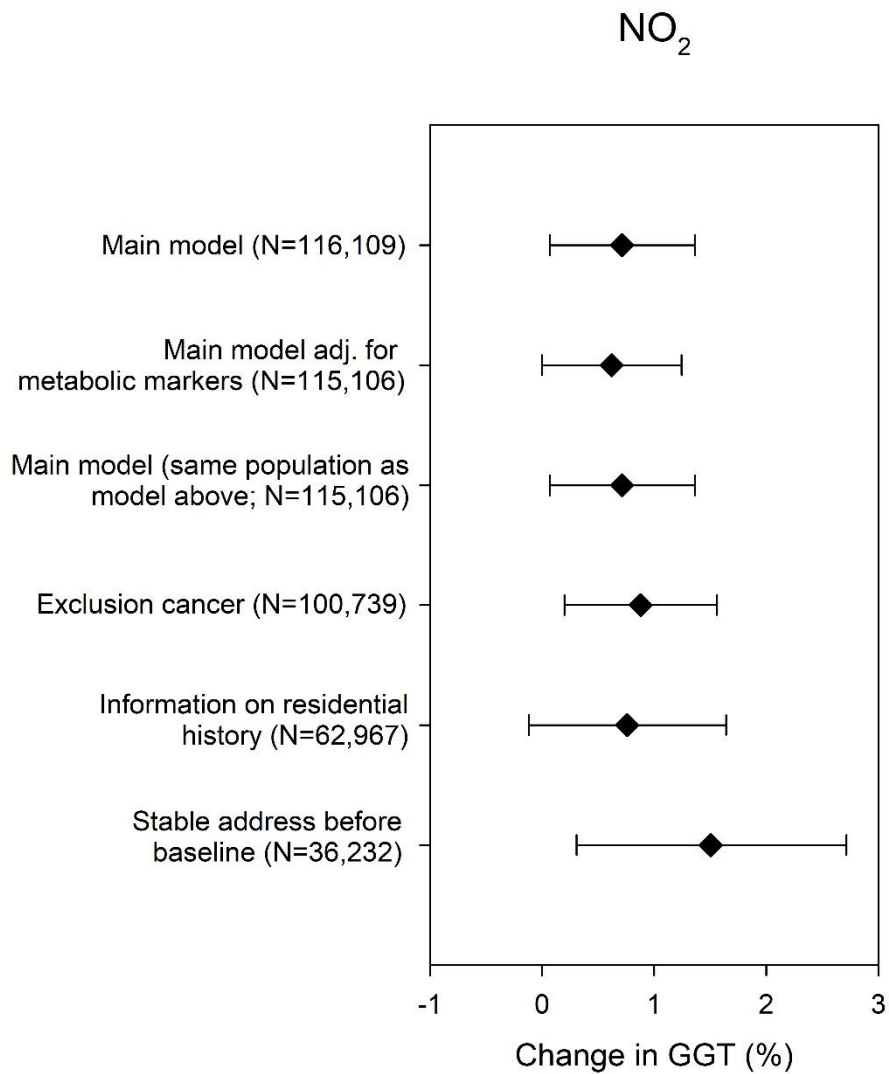


Figure 2a: Sensitivity analyses for associations between serum GGT concentration and NO_2 .

Change (as percentage) in GGT with corresponding 95% CIs for an increment of $10\mu\text{g}/\text{m}^3$. Main model adjusted for calendar year of recruitment, age, sex, BMI, smoking status, individual and neighborhood SES, main model adjusted for metabolic markers was additionally adjusted for glucose, triglycerides and cholesterol; other sensitivity analyses exclude certain sub populations. Residential history was available for 62,967 individuals. Stable address before baseline covers a period of 10 years before baseline.

PM2.5

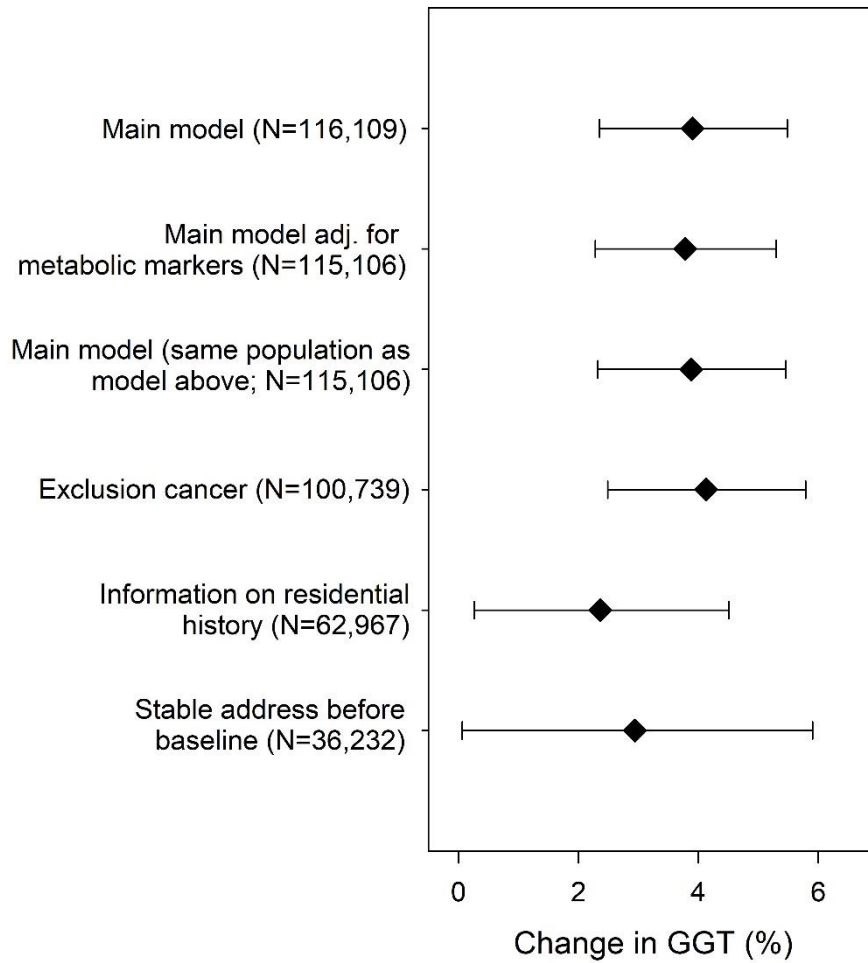
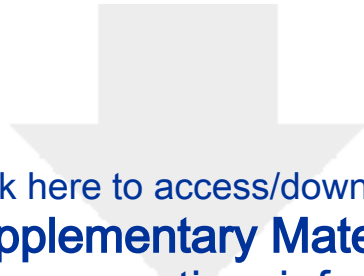


Figure 2b: Sensitivity analyses for associations serum GGT concentration and PM2.5.

Change (as percentage) in GGT with corresponding 95% CIs for an increment of $5 \mu\text{g}/\text{m}^3$. Main model adjusted for calendar year of recruitment, age, sex, BMI, smoking status, individual and neighborhood SES, main model adjusted for metabolic markers was additionally adjusted for glucose, triglycerides and cholesterol; other sensitivity analyses exclude certain sub populations. Residential history was available for 62,967 individuals. Stable address before baseline covers a period of 10 years before baseline.



[Click here to access/download](#)

Supplementary Material

2023_03_21_supporting_information.docx



Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Jan Wirsching: Conceptualization, Methodology, Formal analysis, Software, Writing - original draft, **Gabriele Nagel:** Conceptualization, Resources, Methodology, Validation, Writing - review & editing, **Ming-Yi Tsai:** Data curation, Methodology, Writing - review & editing, **Kees de Hoogh:** Data curation, Methodology, Writing - review & editing, **Andrea Jaensch:** Data curation, Visualization, Writing - review, **Bernhard Anwander:** Methodology, Ressources **Ranjeet S Sokhi:** Conceptualization, Funding acquisition, Methodology, Ressources, **Hanno Ulmer:** Investigation, Resources, review & editing, **Emanuel Zitt:** Resources, review & editing, **Hans Concini:** Resources, review & editing **Bert Brunekreef:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing - review & editing, **Gerard Hoek:** Conceptualization, Funding acquisition, Methodology, Project administration, Validation, Writing - review & editing, **Gudrun Weinmayr:** Conceptualization, Project administration, Supervision, Methodology, Validation, Writing - review & editing;