



Full length article

Joint effects of air pollution and temperature on glycemia: An exposome analysis in European cohorts

A. Jeong^{a,b,*}, J. Edstorp^c, G. Lovison^{a,b}, R. Pickford^d, A. Bergström^c, N. Blay^e, A. Bussalleu^{a,b}, P. Dadvand^f, A. Dalecka^g, M. Imboden^{a,b}, S. Kress^h, Y. Shenⁱ, E. Sochacka-Tatara^j, E. Thiering^d, B. Thorand^{d,k,l}, K. Wolf^d, Z. Yu^c, R. de Cid^e, U. Gehringⁱ, P. Ljungman^c, P. Magnusson^c, O. Mikeš^g, A. Pac^j, H. Pikhart^{g,m}, D. Rizzuto^{c,n}, T. Schikowski^h, M. Standl^d, K. de Hooghⁱ, E. Melén^c, R.C. Vermeulenⁱ, J.J. Vlaanderen^o, G. Pershagen^c, A. Peters^{d,k,p}, N. Probst-Hensch^{a,b,*}

^a Swiss Tropical and Public Health Institute, Allschwil, Switzerland

^b University of Basel, Basel, Switzerland

^c Karolinska Institutet, Stockholm, Sweden

^d Institute of Epidemiology, Helmholtz Zentrum München – German Research Center for Environmental Health (GmbH), Neuherberg, Germany

^e Genomes for Life-GCAT Lab, CORE Program, Germans Trias i Pujol Research Institute (IGTP), Badalona, Spain

^f ISGlobal, Barcelona, Spain

^g RECETOX, Masaryk University, Brno, Czech Republic

^h IUF – Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany

ⁱ Institute for Risk Assessment Sciences, Utrecht University, Utrecht, Netherlands

^j Jagiellonian University Medical College, Chair of Epidemiology and Preventive Medicine, Kraków, Poland

^k Chair of Epidemiology, Institute for Medical Information Processing, Biometry and Epidemiology, Medical Faculty, Ludwig-Maximilians-Universität München, Munich, Germany

^l German Center for Diabetes Research (DZD), Neuherberg, Germany

^m Department of Epidemiology and Public Health, University College London, London, United Kingdom

ⁿ Stockholm University, Stockholm, Sweden

^o National Institute for Public Health and the Environment, Bilthoven, Netherlands

^p German Center for Cardiovascular Research (DZHK e.V.), Munich Heart Alliance – Partner site Munich, Munich, Germany

ABSTRACT

Background: The interdependent long-term effects of a climate-change relevant residential exposome on glycemia in persons without diabetes are not well understood. Applying the exposome analysis approach that we previously developed for lung function, the current analysis aims to identify exposome factors including their joint associations with glycated hemoglobin (HbA1c).

Methods: A pooled dataset of 33'989 measurements of HbA1c collected between 1999 and 2021 from 21'259 participants in two mature birth cohorts and seven adult cohorts were used to assess cross-sectional associations with annual air pollution, greenness, and ambient temperature exposures. Elastic net regression was applied to identify influential exposome features based on a model that *a priori* included all linear and quadratic exposure terms and their two-way interactions. Elastic net regression results were put into the context of single and combined environmental scenarios (improvement of air quality, improvement of greenness, climate change related alterations of ambient temperature).

Results: Elastic net regression of HbA1c stably identified non-zero coefficients for coarse particle concentrations (PM₁₀) and temperature (standard deviation of daily mean temperature) and for their interaction terms, indicating the potential importance of their joint effects. The environmental scenario of improving air quality predicted decreased HbA1c. The environmental scenario assuming climate change-related temperature changes predicted increased HbA1c. The predicted beneficial effects of improving air pollution on glycemia gained in relevance in the presence of climate change, in particular in non-smokers. No non-zero coefficients were found for greenness, neither as main effect nor in interactions with air pollution or temperature.

Conclusion: With respect to metabolic health, our results point to the increasing relevance of improving air quality and meeting WHO guideline values in the era of climate change, particularly in cities where high temperature levels, high levels of air pollution and a high diabetes risk co-occur.

* Corresponding authors at: Swiss TPH, Kreuzstrasse 2, 4123 Allschwil, Switzerland.

E-mail addresses: a.jeong@swisstph.ch (A. Jeong), nicole.probst@swisstph.ch (N. Probst-Hensch).

<https://doi.org/10.1016/j.envint.2026.110538>

Received 20 April 2026; Received in revised form 13 August 2026; Accepted 22 September 2026

Available online 23 September 2026

0160-4120/© 2026 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Diabetes mellitus, the most common metabolic disorder, poses a substantial global health and economic burden. Not considering informal care, the global burden has been estimated to be equivalent to 0.22% of annual global gross domestic product (Chen et al., 2026). Type 2 diabetes mellitus (T2D) accounts for more than 90% of all diabetes cases. Globally, T2D affected 506.0 million individuals in 2021 with numbers projected to increase over the next decades. Persistent hyperglycemia, a characteristic of untreated or uncontrolled T2D, can lead to a range of disabling and partly life-threatening complications (Huang et al., 2025).

In high income countries more than half of hyperglycemia and T2D incidence is the result of behavioral and environmental risk factors. Behavioral factors with a well-established underlying mechanistic pathways are low physical activity, energy-dense diets, high-processed meat diets, low whole grain diets, smoking, and excessive consumption of sweetened beverages or alcohol (Huang et al., 2025; Beulens et al., 2022; Zheng et al., 2018). According to a systematic review, evidence for the association of T2D with ambient and indoor air pollution, residential noise, neighborhood walkability, green space, area-level socio-economic deprivation seems robust, but inconclusive for ambient temperature, neighborhood social environment and food environment (Beulens et al., 2022).

Gaps continue to exist in our understanding of how the complex environment contributes to T2D. First, environmental factors not only affect the risk of T2D directly (e.g. air pollutants, residential noise), but also indirectly by influencing T2D relevant behaviors (e.g. green space and physical activity; neighborhood food retail environment and dietary behavior) (Beulens et al., 2022; den Braver Nicole et al., 2025). By adjusting for potential individual-level mediators, the overall effect of the external environment may be underestimated.

Second, environmental factors irrespective of their correlation likely exhibit additive, synergistic or antagonistic health effects. This is evidenced by multipollutant models of the joint effects of factors such as lack of greenspace, transport related noise, and air pollution on the prevalence or incidence of T2D or its sub-phenotypes (Sørensen et al., 2022; Xi et al., 2026; Klompmaker et al., 2019; Hu et al., 2023). The exposome concept developed by Chris Wild (Wild, 2005) started an era of environmental epidemiology that applies data, biospecimens and novel statistical methods to improve capturing the full complexity of environmental health impacts. Exposome studies on fasting glucose or other glycemia parameters (Liu et al., 2026) and T2D (den Braver Nicole et al., 2025; Ohanyan et al., 2022) that applied more advanced statistical methods for the high-dimensional exposure data are still limited, albeit increasing in number. A recent study examined the cross-sectional association of 85 urban exposome factors at the residential address with the self-reported prevalence of T2D among 14'000 participants in a Dutch primary care cohort. The agnostic approach revealed T2D associations with neighborhood average home values, neighborhood share of non-Western immigrants, surface temperature (non-linear) and green space in a 1 km buffer (non-linear) (Ohanyan et al., 2022).

The disease burden of T2D, a largely preventable disease, is arising primarily from a population at low or moderate disease risk (Geoffrey Rose's Prevention Paradox). Therefore, population-based policies including those targeting the urban environment are most promising and effective (Mackenbach et al., 2025; Haw et al., 2017). To guide policies, it is important to consider the environment in its exposome complexity. Evidence is, on the one hand, needed on the potential impact of addressing specific exposure domains and, on the other hand, on the dependency of the achievable impact on parallel changes in other exposure domains. In the era of climate change and its broad environmental consequences, this health-in-all-policy perspective further gains in relevance.

In this study, we applied an exposome analysis approach that we previously developed for lung function (Jeong et al., 2025) to identify

strongest exposome factors including their joint associations within a priori selected climate change relevant exposure domains (air pollution, greenness, temperature) for glycated hemoglobin (HbA1c). T2D diagnosis to some extent depends on healthcare access and diagnosis methods, which may correlate with environmental factors, but HbA1c among persons without diabetes might be less susceptible to such bias and suit better our primary interest in the contribution of the exposome to disease development.

2. Methods

2.1. Study population

We combined HbA1c data from 9 population-based cohorts in six European countries: two mature birth cohorts BAMSE (Sweden) and PIAMA (Netherlands); and seven adult cohorts GCAT (Spain), HAPIEE (Czech Republic), KORA (Germany), SALIA (Germany), SALT (Sweden), SAPALDIA (Switzerland), and SNAC-K (Sweden). More detailed descriptions of the cohorts are provided in the [Supplementary material](#).

This study included participants without any indication of past or current diabetes (no self-reported diabetes diagnosis, no self-reported use of diabetes medication, no registry-confirmed diabetes diagnosis, HbA1c < 6.5%, fasting glucose < 126 mg/dl, or random glucose < 200 mg/dl).

Participants with missing information on HbA1c, external exposome features, and *a priori* selected set of covariates (age, sex, smoking status, marital status, employment, and education level for adult cohorts; age, sex, smoking status, parental education for mature birth cohorts) were excluded. Missingness in body mass index (BMI), only considered in sensitivity analysis, was not considered as exclusion criterion and was low (N = 378, 1.1%). Participants with suggestive outliers for HbA1c measurement were excluded (<3.6%, i.e. equivalent to 3 times the interquartile range below the 25th percentile) (N = 10, 0.03%).

A total of 33'989 observations from 21'259 participants were analyzed. Different numbers of repeated HbA1c measurements for the time period with available exposome data were included per cohort: one survey from BAMSE (2020–2021), GCAT (2016–2018), HAPIEE (2003–2005), SALIA (2007–2008), and SALT (2004–2008); three surveys from KORA (1999–2001, 2006–2008, 2013–2014), PIAMA (2004–2005, 2008–2011, 2012–2014), and SAPALDIA (2001–2003, 2010–2011, 2016–2018); and six surveys from SNAC-K (2001–2004, 2004–2007, 2007–2010, 2010–2013, 2013–2016, 2016–2019).

2.2. HbA1c z-scores

HbA1c was measured either in venous or capillary blood. Based on the observation that the distribution of HbA1c did not differ by age groups (Fig. S1), HbA1c from mature birth cohorts and adult cohorts were analyzed in a single pooled model. To reduce bias due to different methods in HbA1c measurement (e.g. blood type; instrument), a rank-based method rather than the nominal HbA1c values was applied for defining the primary outcome. Z-scores were calculated by rank-based inverse normal transformation, following the equation (Yang et al., 2012):

$$z = \Phi^{-1} \left(\frac{x - 0.5}{N} \right)$$

where x means the original HbA1c values, and z means the transformed HbA1c values, i.e. z-scores. The z-score calculation was done by cohort and survey so that each individual was assigned a value at each time point, while the values are independent of cohort membership. The original HbA1c and the z-score distribution are illustrated in Fig. 1.

2.3. External exposome

Following a previous analysis within EXPANSE with lung function as outcome (Jeong et al., 2025), we assessed associations of HbA1c with external exposome features in the domains of air pollution, greenness, and temperature (Table 1). All exposure features except noise, which was considered as secondary exposure only, were derived from the pan-European models developed in the EXPANSE project (de Hoogh et al., 2025) (Table S1). Each exposure variable was standardized to have 0 mean and 1 standard deviation.

2.3.1. Primary exposure: Air pollution

Annual mean exposure to NO₂ (“no2”), PM_{2.5} (“pm25”), and PM₁₀ (“pm10”) were estimated from geographically and temporally weighted regression models (Shen et al., 2022). Each individual was assigned a 365-day average using the annual mean exposure at the home address for the year of blood sampling and the year before, following the equation:

$$x_i = (n_{y_0,i}x_{y_0,i} + (365 - n_{y_0,i})x_{y_0-1,i})/365$$

where y_0 is the year of blood sampling; $n_{y_0,i}$ is the number of days passed before the blood sampling in the year y_0 ; $x_{y_0,i}$ is the annual mean exposure of the year of blood sampling at the home address of the individual i ; $x_{y_0-1,i}$ is the annual mean exposure of the previous year of blood sampling at the home address of the individual i .

Unlike in Jeong et al (Jeong et al., 2025), ozone exposure was no longer considered. In Europe, ozone consistently shows strong negative correlation with other air pollutants and null or negative associations with mortality and cardiovascular disease risk, likely not due to ozone being protective, but due to complex spatial and environmental confounding, making its interpretation challenging (Brunekreef et al.,

Table 1

Abbreviations and description of the exposome variables used in this study.

Abbreviation	Description
gsc	Euclidean distance to the nearest green space in meter using Corine Land Cover database of the nearest year of blood sampling (available for 2000, 2006, 2012, and 2018)
ndvi5	Mean Normalized Difference Vegetation Index within 500 m buffer of the nearest year of blood sampling (available for 2000, 2005, 2010, 2015, and 2020)
no2	Nitrogen dioxide in $\mu\text{g}/\text{m}^3$, 365-day average before blood sampling derived from annual mean of the year of blood sampling and the year before (available for every year between 2000 and 2019)
pm10	Particulate matter with aerodynamic diameter equal to or less than $10 \mu\text{m}$ in $\mu\text{g}/\text{m}^3$, 365-day average before blood sampling derived from annual mean of the year of blood sampling and the year before (available for every year between 2000 and 2019)
pm25	Particulate matter with aerodynamic diameter equal to or less than $2.5 \mu\text{m}$ in $\mu\text{g}/\text{m}^3$, 365-day average before blood sampling derived from annual mean of the year of blood sampling and the year before (available for every year between 2000 and 2019)
tav	365-day average of daily mean temperature in $^{\circ}\text{C}$ before blood sampling (available for every day between 2003 and 2020)
tsd	365-day standard deviation of daily mean temperature in $^{\circ}\text{C}$ before blood sampling (available for every day between 2003 and 2020)

2021).

2.3.2. Primary exposure: Greenness

Mean Normalized Difference Vegetation Index (NDVI) within a 500 m buffer around the residential address (“ndvi5”) was estimated from the Vegetation Indices (MOD13Q1) product of the Terra Moderate Resolution Imaging Spectroradiometer (MODIS) with 250 m x 250 m resolution for the years 2000, 2005, 2010, 2015, and 2020. Euclidian distance to the nearest green space (“gsc”) from the residential address

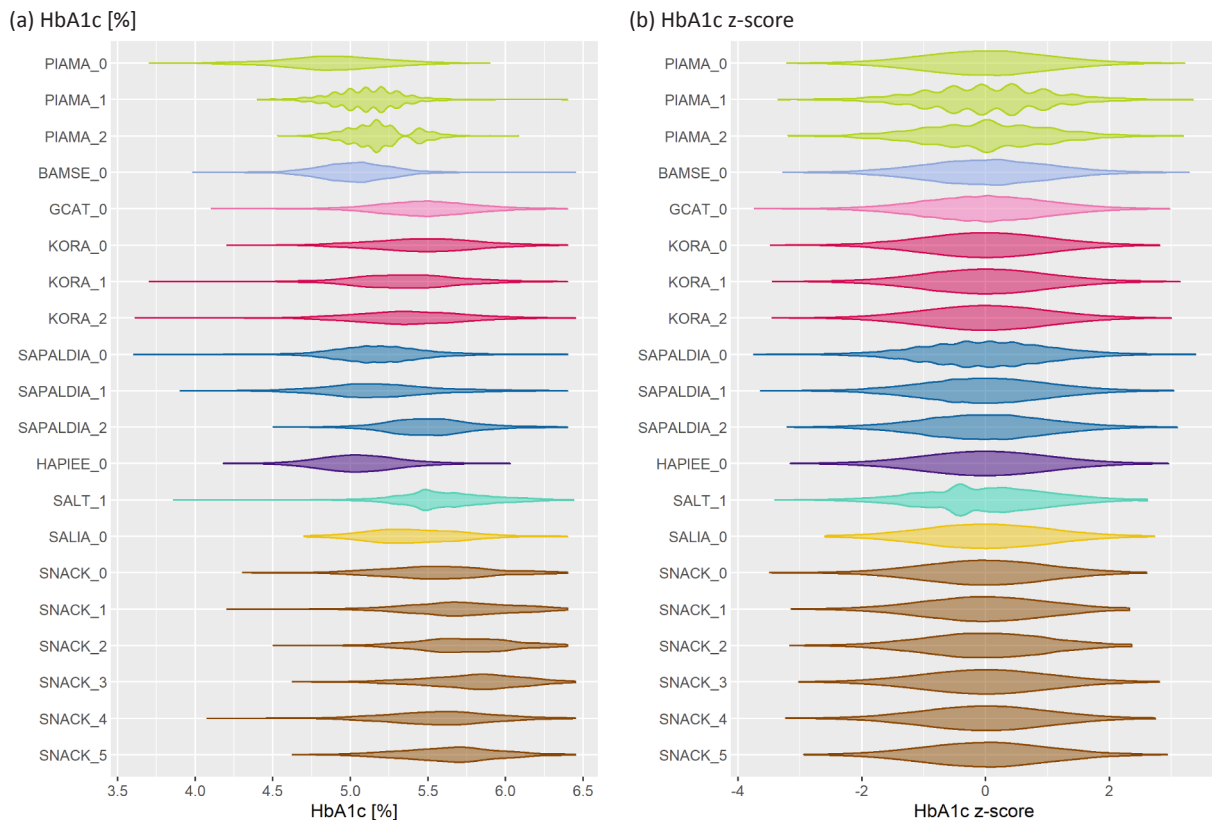


Fig. 1. Distribution of nominal HbA1c (a) and HbA1c z-score (b), by cohort and survey.

was calculated using Corine Land Cover database for the years 2000, 2006, 2012, and 2018 (de Hoogh et al., 2025).

The greenness estimate from the nearest available year was assigned to each individual's home address. If the blood sampling took place exactly in the middle of the interval, the year preceding the blood sampling was preferred.

2.3.3. Primary exposure: Temperature

Daily mean temperature between 2003 and 2020 was estimated by a pan-European model utilizing ambient temperature monitoring networks, remote sensing, and land use data (Bussalieu et al., 2024). 365-day average of the daily mean temperature before the date of blood sampling ("tav") and 365-day standard deviation of the daily mean temperature ("tsd") were assigned to each individual at their home address.

$$tav_i = \sum_d tmp_{avg_{d,i}} / 365$$

$$tsd_i = \sum_d (tmp_{avg_{d,i}} - tav_i)^2 / 365$$

where $tmp_{avg_{d,i}}$ means daily mean temperature for the day d at the home address of individual i . d ranges from 1 to 365 days before blood sampling.

For blood sampled in 2003 or earlier, daily temperature estimates for 365 days before blood sampling were not available. In these cases, daily temperature estimates from 2003 were used to derive tav and tsd.

2.3.4. Secondary exposure: Noise

At the time point of the current analysis, there is no pan-European harmonized noise model available for the study areas involved. Therefore, we utilized noise estimates from local models. For a subset of cohorts, i.e. KORA, PIAMA, SALT, SAPALDIA, and SNAC-K, annual average day-evening-night noise levels ("lden") were calculated for traffic-related noise. Annual mean lden estimate was assigned to each individual at their home address for the year blood sampling took place or the nearest available year. Given the limited availability of noise estimates, we considered noise as a secondary exposure and did not include it in the main analysis. Instead, we assessed if adjustment for noise would change associations between HbA1c and primary exposures in the single exposure models.

2.4. Covariates

We included covariates that are considered potentially confounding, but unlikely mediating the association between exposome and glycemia. Age in years was standardized to have 0 mean and 1 standard deviation. Linear, quadratic, and cubic terms of standardized age were included in the models. Sex was coded as female vs male. Smoking status was coded as smoker vs non-smoker (former- or never-smoker). PIAMA participants were assumed to be non-smokers at age 8 and 12 years. Marital status was coded as single (including divorced or widowed) vs married. Employment status was coded as employed vs otherwise (unemployed or retired). Marital status and employment status were not considered in the mature birth cohorts. Education level was coded as low vs moderate vs high. For the mature birth cohorts, individual education was replaced by paternal and maternal education, which was coded as low vs moderate vs high vs unknown. Population density was included as a continuous variable. Covariates, except for sex and parental education, were considered time-varying and therefore defined at each year of blood sampling.

2.5. Single exposure models for the seven exposome variables

HbA1c z-score was regressed on each of the seven exposome

variables adjusting for age (linear, quadratic, and cubic terms), sex, smoking status, marital status (adult cohorts only), employment status (adult cohorts only), individual's education (adult cohorts only), paternal and maternal education (mature birth cohorts only), and population density. Gaussian linear regression was applied per cohort, and linear mixed effects models were applied for cohorts with multiple surveys with random intercepts for participants. The pooled models were additionally adjusted for cohort as fixed effect.

2.5.1. Single exposure models including noise

To justify not to include noise in the elastic net regression models, the single exposure models were fitted again with additional adjustment for noise. This analysis was restricted to observations with noise estimates available ($N = 26,592$).

2.6. Elastic net regression

We applied elastic net regression as described previously (Jeong et al., 2025) to identify the exposome features that show the strongest association with HbA1c z-scores.

Step 0. Linear mixed effects model.

Residuals of the HbA1c z-scores were derived from linear mixed effects models adjusted for the same set of covariates as for the single exposure models described above. Random intercepts for participants were included to account for repeated measurements.

Step 1. Elastic net regression allowing shrinkage for all exposome features.

The residuals from Step 0 were used as the outcome variable as a single pooled dataset for elastic net regression. It was regressed on linear and quadratic terms of the seven exposome variables as well as their two-way interactions (total number of predictors $N_p = 35$). The mixing parameter alpha as well as the penalizing parameter lambda was determined by a cross-validation. The optimal alpha was defined as the value with which cross-validation error was at the minimum. The optimal lambda was defined as the largest value such that cross-validation error was within 1 standard error of the minimum. The final penalty term was calculated as $\lambda \times (\alpha \times L1\text{-norm} + (1-\alpha)/2 \times L2\text{-norm})$.

Step 2. Elastic net regression without shrinkage for the variables selected in Step 1 and their lower order terms.

Elastic net regression was fitted again but assigning zero penalty (no shrinkage) to (i) the variables for which Step 1 elastic net identified non-zero coefficients and (ii) their lower order terms. For example, the interaction term of pm25 and tav, but not their lower order terms had a non-zero coefficient in Step 1; its lower order terms pm25 and tav were forced into the final model. The optimal lambda was searched again by cross-validation. In rare occasions when additional high order terms were selected in Step 2, their corresponding lower order terms were again forced into the model. This is to prevent second order terms but not their lower order terms being included in the final model, which would hinder interpretation.

The coefficients of the elastic net regression refer to the effect estimates by 1 standard deviation change in the corresponding exposure, conditional on all other variables.

Performance of the elastic net regression was assessed by 10-fold cross-validation. The total observations were randomly assigned to 10 groups. Within each of the 10 iterations, one group was set aside (a test set), and the entire procedure of the two-step elastic net regression was applied to the remaining 9 groups (a training set). Stability of the selection of non-zero coefficients across 10 groups was visualized and inspected qualitatively. If the 10-fold cross-validation showed reasonable stability (at least 6 times out of the 10 folds), the elastic net regression using the total observations was reported and interpreted further.

2.7. Interpretation of elastic net regression results

To facilitate the interpretation of the elastic net regression results, we applied two approaches: first we calculated Shapley additive explanation (SHAP) values to each of the exposome variables, and second we applied an environmental scenario approach similar to Jeong et al (Jeong et al., 2025).

2.7.1. Shapley additive explanations

SHAP values represent the contribution of a specific variable to the prediction. In brief, SHAP values are calculated as the difference between the outcome value predicted from the final model and the expected prediction if the value of a specific variable from the final model is unknown (Strumbelj and Kononenko, 2014). We calculated the approximated SHAP values for the final elastic net regression model, using Monte Carlo simulation as described in Strumbelj and Igor (Strumbelj and Kononenko, 2014). SHAP values are calculated for each observation, and the average of the absolute SHAP values over all predictions are reported to inform the relative importance of the exposome variables to explain HbA1c.

2.7.2. Effect estimates in the context of different environmental scenarios

This is to calculate effect estimates by assuming *a priori* determined increments in various exposures, compared to the observed mean exposures. The assumed increments differ by scenario: scenario 1 “improving air quality” assumes reduction in NO₂ and PM₁₀ by 10 µg/m³ and in PM_{2.5} by 5 µg/m³; scenario 2 “increasing greenness” assumes increase in NDVI by 0.1 and reduction in the distance to the nearest green space by 100 m; scenario 3 “climate change” assumes increase in 365-day average of daily mean temperature by 0.5 °C and 365-day standard deviation of daily mean temperature by 1 °C. Scenario 4 “improving air quality in the presence of climate change” and the scenario 5 “increasing greenness in the presence of climate change” are defined as combinations of the scenarios 1 and 3, and the scenarios 2 and 3, respectively (Table 2).

2.8. Sensitivity analyses

First, while we *a priori* abstained from adjusting models for adiposity, a potential mediator of exposome effects, we hypothesized that adiposity may affect the exposome-glycemia association. To explore this hypothesis, the elastic net regression was stratified by BMI cutoff 25 kg/m² or equivalent age- and sex-specific adiposity cutoffs for the participants below 18 years (PIAMA). Second, the exposome features may have different characteristics (e.g. types of greenness; heat island effects) or induce different behaviors in urban and non-urban areas. We therefore stratified the elastic net regression by a binary urbanicity indicator

(urban vs non-urban), which was derived from population density based on cohort-specific median values. This data-driven stratification assists within-cohort comparison, which is not subject to differences in statistical power. Third, the elastic net regression was stratified by smoking status (smoker vs non-smoker (never- and ex-smoker combined)), to explore the effect modification by smoking. All stratified analyses were adjusted for the same set of covariates as for the main analysis, except for the smoking-stratified analysis which was not adjusted for smoking status. The urbanicity-stratified analysis was still adjusted for population density as continuous variable. Similar to the 10-fold cross-validation described above, stratified analyses were conducted by segregating data into different strata and applying the entire two-step elastic net regression procedure to each stratum.

All statistical analyses were conducted using R v4.4 (Team RC, n.d), including packages “glmnet” (Friedman et al., 2010), “lme4” (Bates et al., 2015), and “fastshap” (Brandon, 2019) for elastic net regression, linear mixed effects models, and fast approximation of SHAP values, respectively.

3. Results

We examined 33'989 measurements of HbA1c from 21'259 participants in two mature birth cohorts and seven adult cohorts. Study sample characteristics are reported in Table 3 and age distribution per cohort and survey is illustrated in Fig. S2. PIAMA participants were the youngest irrespective of survey and SALIA participants were the oldest at the earliest survey. SNAC-K provided the most densely repeated measurements up to the oldest age range. Females are generally overrepresented. SALIA, a cohort of exclusively elderly women, showed the lowest rate of smoking. The proportion of not employed or retired participants was higher in older cohorts such as SALIA and SNAC-K. Population density strongly varied by cohort with GCAT, a Spanish cohort, being the most populated. Fig. 2 shows the exposure distribution per cohort and survey. Air pollution concentrations tended to decrease over time. HAPIEE participants were exposed to highest concentrations of particulate matter. GCAT and SNAC-K participants were exposed to lower greenness. SNAC-K participants lived farthest away from green space. Temperature variables varied widely across cohorts, with average temperature being highest in GCAT. Spearman correlation between exposome features per cohort and survey is reported in Fig. S3. While inverse and mostly strong correlation between NDVI and air pollution were observed for most cohorts, weak correlations between NDVI and particulate matter air pollution were observed in HAPIEE.

Fig. S4 shows cohort-specific and pooled results from single exposure models. Particulate matter (pm25, pm10) and tsd were associated with higher HbA1c z-score in pooled analysis, while the association was not consistent in cohort-specific analyses. As shown in Fig. S5, noise adjustment resulted in little differences in the association of any exposure with HbA1c z-score. This supported our decision not to include noise in elastic net regression.

As shown in Fig. 3, the elastic net regression identified non-zero coefficients for particulate matter (pm25, pm10) and temperature variables (tav, tsd) including quadratic terms of pm10 and tsd (pm10sq, tsdsq) and interactions between particulate matter and temperature (pm25_tav and pm10_tsd). All lower order terms except tsd were forced into the model due to their second order terms. The mean absolute SHAP values indicate that pm25_tav, tsd, and tsdsq make the biggest contribution to the HbA1c z-score prediction. However, pm25_tav was not stably selected in the 10-fold cross-validation, and therefore needs to be interpreted with caution. The forced lower order terms made smaller contributions. The 10-fold cross-validation provided an evaluation of the selection stability. One of the second order terms (tsdsq) and one first order term (tsd) were most stably selected (9 times out of the 10 folds) in the 10-fold cross-validation (Fig. 3 and Table S2).

Table 4 summarizes the results in the context of different environmental scenarios. The “improving air quality” scenario was associated

Table 2
Assumed changes in exposures in different environmental scenarios.

Scenario	Assumed changes in exposures						
	no2	pm25	pm10	ndvi5	gsc	tav	tsd
1. Improving air quality	-10	-5	-10	0	0	0	0
2. Increasing greenness	0	0	0	+0.1	-100	0	0
3. Climate change	0	0	0	0	0	+0.5	+1
4. Improving air quality in the presence of climate change	-10	-5	-10	0	0	+0.5	+1
5. Increasing greenness in the presence of climate change	0	0	0	+0.1	-100	+0.5	+1

Values are in original units: µg/m³ for no2, pm25, pm10; m for gsc; °C for tav, tsd.

Table 3
Study sample characteristics per cohort and survey.

(a) Mature birth cohorts											
Cohort			BAMSE		PIAMA						
N			985		780		1254		708		
Year of blood sampling			2020–2021		2004–2005		2008–2011		2012–2014		
Age [years]			25.8 (0.8)		8.1 (0.3)		12.7 (0.4)		16.3 (0.2)		
Sex		Female	612 (62.1)		386 (49.5)		625 (49.8)		356 (50.3)		
		Male	373 (37.9)		394 (50.5)		629 (50.2)		352 (49.7)		
Smoking status		Smoker	188 (19.1)		0 (0.0)		0 (0.0)		105 (14.8)		
		Non-smoker (former/never)	797 (80.9)		780 (100.0)		1254 (100.0)		603 (85.2)		
Paternal education		Low	556 (56.4)		7 (0.9)		18 (1.4)		9 (1.3)		
		Moderate	204 (20.7)		208 (26.7)		361 (28.8)		235 (33.2)		
		High	225 (22.8)		118 (15.1)		207 (16.5)		126 (17.8)		
		Unknown	0 (0.0)		447 (57.3)		668 (53.3)		338 (47.7)		
Maternal education		Low	572 (58.1)		7 (0.9)		6 (0.5)		2 (0.3)		
		Moderate	181 (18.4)		218 (27.9)		361 (28.8)		243 (34.3)		
		High	232 (23.6)		70 (9.0)		143 (11.4)		82 (11.6)		
		Unknown	0 (0.0)		485 (62.2)		744 (59.3)		381 (53.8)		
Population density*			57.8 (50.8)		27.4 (16.3)		27.0 (16.1)		25.6 (16.6)		
HbA1c [%]			5.0 (0.2)		4.9 (0.3)		5.1 (0.2)		5.2 (0.2)		
(b) Adult cohorts											
Cohort			GCAT	HAPIEE	KORA		SALIA		SALT		
N			5464	632	2032	1789	1829	316	1579		
Year of blood sampling			2016–2018	2003–2005	1999–2001	2006–2008	2013–2014	2007–2008	2004–2008		
Age [years]			50.3 (7.6)	57.6 (7.2)	46.3 (12.2)	51.2 (10.7)	59.1 (12.1)	74.1 (2.6)	63.6 (8.6)		
Sex		Female	3230 (59.1)	320 (50.6)	1051 (51.7)	950 (53.1)	964 (52.7)	316 (100.0)	922 (58.7)		
		Male	2234 (40.9)	312 (49.4)	981 (48.3)	839 (46.9)	865 (47.3)	0 (0.0)	648 (41.3)		
Smoking status		Smoker	992 (18.2)	161 (25.5)	466 (22.9)	334 (18.7)	282 (15.4)	9 (2.8)	258 (16.4)		
		Non-smoker (former/never)	4472 (81.8)	471 (74.5)	1566 (77.1)	1455 (81.3)	1547 (84.6)	307 (97.2)	1312 (83.6)		
Marital status		Single	1627 (29.8)	159 (25.2)	505 (24.9)	406 (22.7)	472 (25.8)	125 (39.6)	441 (28.1)		
		Married	3837 (70.2)	473 (74.8)	1527 (75.1)	1383 (77.3)	1357 (74.2)	191 (60.4)	1129 (71.9)		
Employment status		Employed	4169 (76.3)	355 (56.2)	1440 (70.9)	1664 (93.0)	1713 (93.7)	7 (2.2)	1074 (68.4)		
		Not employed/retired	1295 (23.7)	277 (43.8)	592 (29.1)	125 (7.0)	116 (6.3)	309 (97.8)	496 (31.6)		
Education		Low	471 (8.6)	61 (9.7)	978 (48.1)	817 (45.7)	847 (46.3)	48 (15.2)	367 (23.4)		
		Moderate	2748 (50.3)	494 (78.2)	528 (26.0)	485 (27.1)	490 (26.8)	166 (52.5)	589 (37.5)		
		High	2245 (41.1)	77 (12.2)	526 (25.9)	487 (27.2)	492 (26.9)	102 (32.3)	614 (39.1)		
Population density*			141.1 (100.1)	27.3 (9.0)	24.2 (17.8)	24.4 (17.9)	24.5 (17.9)	26.5 (13.7)	42.5 (43.2)		
HbA1c [%]			5.5 (0.3)	5.1 (0.3)	5.5 (0.3)	5.4 (0.3)	5.4 (0.3)	5.4 (0.3)	5.6 (0.3)		
Cohort			SAPALDIA		SNAC-K						
N			5779	3791	1515	2132	593	1311	397	811	301
Year of blood sampling			2001–2003	2010–2011	2016–2018	2001–2004	2004–2007	2007–2010	2010–2013	2013–2016	2016–2019
Age [years]			51.7 (11.4)	58.6 (10.9)	67.9 (8.0)	73.6 (10.9)	84.2 (7.1)	76.9 (10.3)	85.3 (7.4)	80.3 (9.8)	86.2 (8.2)
Sex		Female	2984	1872	771 (50.9)	1370 (64.3)	409 (69.0)	803 (61.3)	249 (62.7)	488 (60.2)	181 (60.1)
			(51.6)	(49.4)							
		Male	2795	1919	744 (49.1)	762 (35.7)	184 (31.0)	508 (38.7)	148 (37.3)	323 (39.8)	120 (39.9)
			(48.4)	(50.6)							
Smoking status		Smoker	1433	655 (17.3)	203 (13.4)	307 (14.4)	62 (10.5)	213 (16.2)	54 (13.6)	138 (17.0)	40 (13.3)
			(24.8)								
		Non-smoker (former/never)	4346	3136	1312	1825 (85.6)	531 (89.5)	1098 (83.8)	343 (86.4)	673 (83.0)	261 (86.7)
			(75.2)	(82.7)	(86.6)						
Marital status		Single	1734	1187	521 (34.4)	1190 (55.8)	394 (66.4)	662 (50.5)	217 (54.7)	396 (48.8)	138 (45.8)
			(30.0)	(31.3)							
		Married	4045	2604	994 (65.6)	942 (44.2)	199 (33.6)	649 (49.5)	180 (45.3)	415 (51.2)	163 (54.2)
			(70.0)	(68.7)							
Employment status		Employed	4048	2296	504 (33.3)	476 (22.3)	26 (4.4)	363 (27.7)	28 (7.1)	271 (33.4)	42 (14.0)
			(70.0)	(60.6)							
		Not employed/retired	1731	1495	1011	1656 (77.7)	567 (95.6)	948 (72.3)	369 (92.9)	540 (66.6)	259 (86.0)
			(30.0)	(39.4)	(66.7)						
Education		Low	362 (6.3)	180 (4.7)	52 (3.4)	569 (26.7)	209 (35.2)	300 (22.9)	115 (29.0)	171 (21.1)	76 (25.2)
		Moderate	3769	2429	940 (62.0)	830 (38.9)	246 (41.5)	531 (40.5)	179 (45.1)	323 (39.8)	125 (41.5)
			(65.2)	(64.1)							
		High	1648	1182	523 (34.5)	733 (34.4)	138 (23.3)	480 (36.6)	103 (25.9)	317 (39.1)	100 (33.2)
			(28.5)	(31.2)							
Population density*			32.7 (34.9)	30.0 (33.5)	30.2 (33.7)	116.6	113.3	109.4	111.8	106.9	108.6
						(43.6)	(44.4)	(49.8)	(47.2)	(51.9)	(47.3)
HbA1c [%]			5.2 (0.3)	5.2 (0.4)	5.5 (0.3)	5.6 (0.4)	5.7 (0.3)	5.7 (0.3)	5.8 (0.3)	5.6 (0.3)	5.6 (0.3)

Continuous variables presented as mean (standard deviation) and categorical variables as count (%).

* Focal mean within 1500m square

with lower HbA1c z-score, while a higher HbA1c z-score was predicted in the “climate change” scenario. The benefit of improving air quality increased when climate change was assumed at the same time. Increasing greenness appeared irrelevant, as no non-zero coefficient was

found for any greenness-related variables.

When stratified by urbanicity, 10-fold cross-validation did not show any stable non-zero coefficients in the non-urban stratum, while the non-zero coefficients identified in the urban stratum were comparable to the

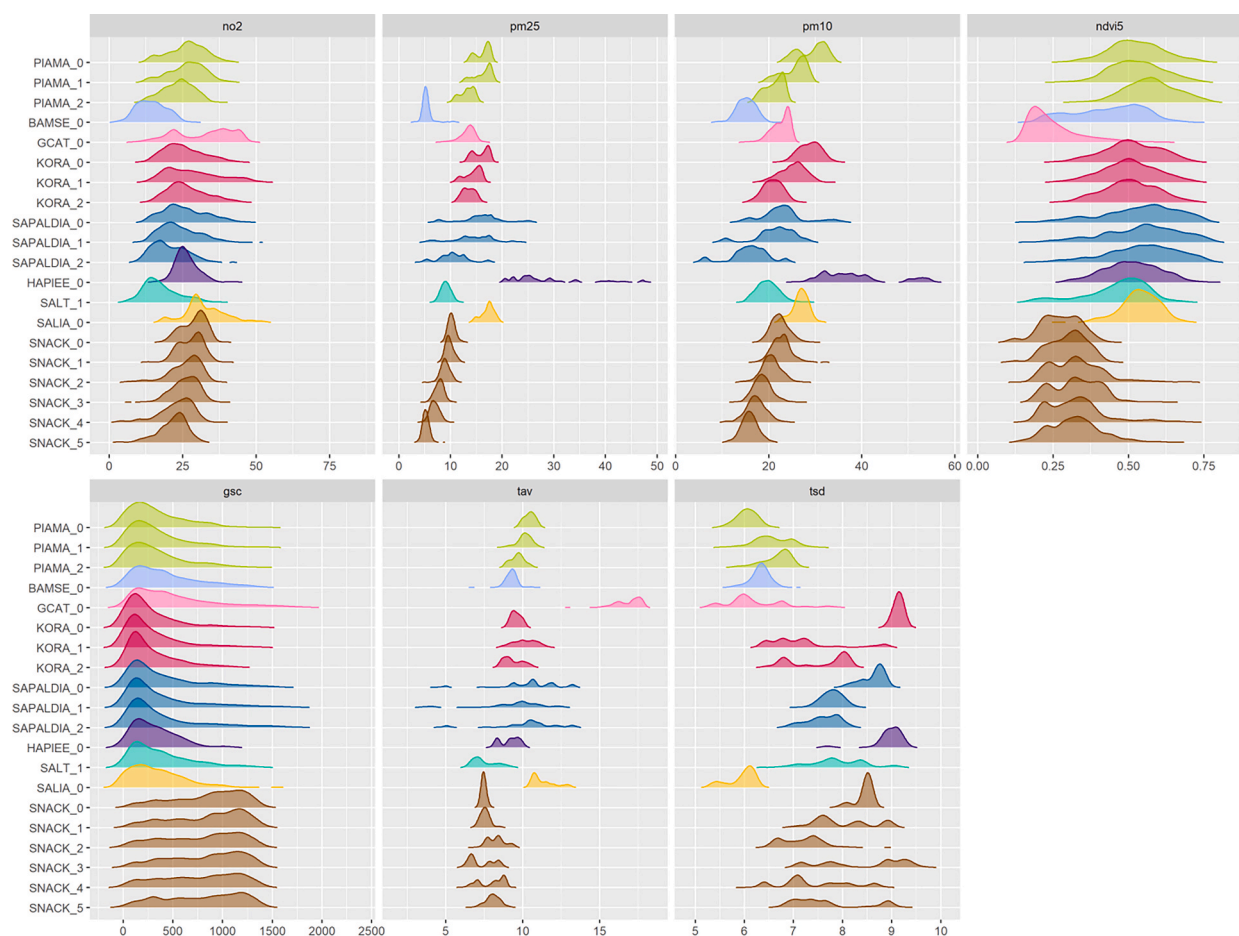


Fig. 2. Exposure distribution per cohort and survey Units in x-axis: $\mu\text{g}/\text{m}^3$ for no2, pm25, pm10; m for gsc; $^{\circ}\text{C}$ for tav, tsd.

main analysis albeit slightly less stable (Fig. 4 and S6). The SHAP analysis identified tsdsq and tsd as the biggest contributors in urban areas, similar to the main model. The scenario analysis restricted to urban areas showed similar pattern as in the main model but smaller benefits of air quality improvement (Table 4). BMI-stratified analysis found no stable non-zero coefficients in both strata (Fig. S7). From the smoking stratified analysis, tsd, pm10, their interaction, and tsdsq were stably selected in non-smokers, while 10-fold cross-validation did not provide any stable non-zero coefficients in smokers (Fig. 5 and S8). In non-smokers, tsd and tsdsq were found with larger coefficients as well as with larger mean absolute SHAP values than in the main model (Fig. 5). This was in line with the larger predicted increase of HbA1c in non-smokers than in the main model suggested in the climate change scenario analysis (Table 4).

4. Discussion

As part of the EXPANSE project (de Hoogh et al., 2025; Vlaanderen et al., 2021), the current analysis expands the approach previously applied to lung function (Jeong et al., 2025) to glycated hemoglobin (HbA1c) as a T2D-related health endpoint. It capitalizes on harmonized pan-European exposure maps (de Hoogh et al., 2025) and European-wide cohort participants broadly characterized for T2D phenotypes, which allowed restricting the study sample to participants without any indication of past or present diabetes. This offered the opportunity to focus on environmental risks likely impacting disease incidence rather than access to care and disease control.

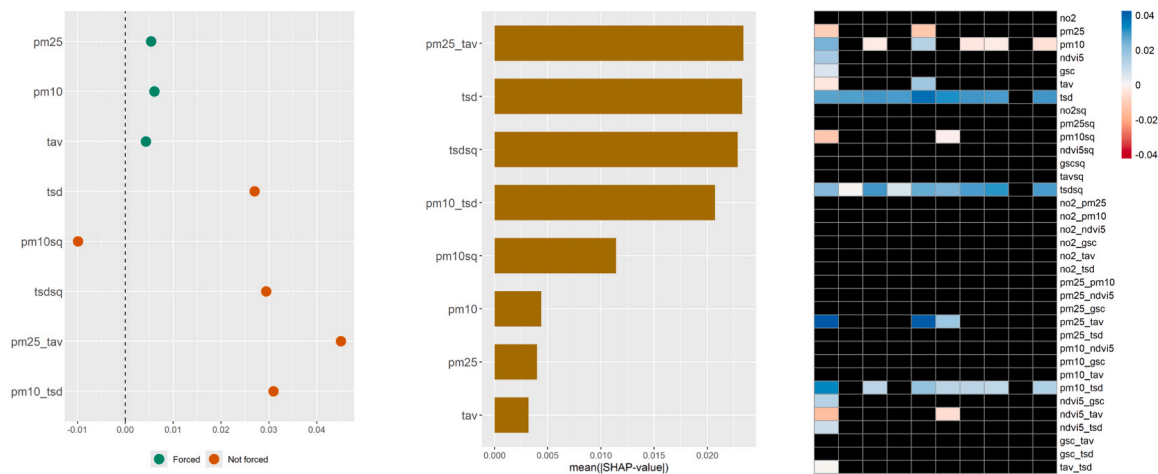
The results of this cross-sectional study, irrespective of whether derived from the single exposure models or the elastic net models, point

to positive associations of HbA1c with both exposure to particulate matter and temperature in persons without diabetes. The observed associations of HbA1c with particulate matter and temperature as well as their interaction are in line with observations from previous epidemiological studies.

Recent meta-analyses reported associations of HbA1c (Tian et al., 2022) and T2D risk (Parasin et al., 2025) with long-term ambient $\text{PM}_{2.5}$, PM_{10} , and NO_2 exposures, yet pointed to considerable heterogeneity between studies. These inhaled pollutants have shown to induce systemic inflammation and interfere with glucose metabolism and induced insulin resistance (Gong et al., 2024; Liu et al., 2025).

4.1. PM_{10} may be more relevant than NO_2 or $\text{PM}_{2.5}$

Interestingly, in the present analysis, PM_{10} rather than NO_2 or $\text{PM}_{2.5}$ showed consistent associations with HbA1c, which is also in line with the previously reported evidence. A dose-response relationship in the association with T2D risk was observed for PM_{10} and not for NO_2 or $\text{PM}_{2.5}$, suggesting that this pollutant may have a strong metabolic effect (Parasin et al., 2025). Exposure routes for ambient PM are not restricted to inhalation, which is the primary exposure route of interest in lung function. In particular larger particles such as PM_{10} that are more likely trapped in the upper and middle airways are moved upward to the oral cavity, where they are then swallowed (Gao et al., 2025). This exposure route may be of particular relevance to the increasing body of evidence suggesting that air pollutants may impact T2D risk by altering gut microbiota (Bailey et al., 2020).



Effect estimates by 1 standard deviation change in the corresponding exposure, conditional on all other variables.

* Residuals from a linear mixed effects model, adjusted for age (linear, quadratic, and cubic terms), sex, smoking status, marital status, employment status, individual education, population density, and cohort. For BAMSE and PIAMA, the model was not adjusted for marital status, employment status, and individual education, but for parental education instead.

** Approximated SHAP values were calculated based on the Monte Carlo simulation and their absolute values were averaged over all predictions to represent the contribution of each variable to the prediction. Only the variables with non-zero coefficients are plotted.

*** Total observations were randomly assigned to 10 groups. Within each of the 10 iterations, one group was set aside (a test set), and the entire procedure of the two-step elastic net regression was applied to the remaining 9 groups (a training set). Each column represents the results of each iteration. Black cells indicate zero coefficients.

Forced = elastic net regression did not identify non-zero coefficient but forced due to their corresponding higher order term(s).

Not forced = elastic net regression identified non-zero coefficient.

Fig. 3. Non-zero coefficients from elastic net regression of exposome features on HbA1c z-score*, mean absolute SHAP values**, and 10-fold cross-validation results*** Effect estimates by 1 standard deviation change in the corresponding exposure, conditional on all other variables. * Residuals from a linear mixed effects model, adjusted for age (linear, quadratic, and cubic terms), sex, smoking status, marital status, employment status, individual education, population density, and cohort. For BAMSE and PIAMA, the model was not adjusted for marital status, employment status, and individual education, but for parental education instead. ** Approximated SHAP values were calculated based on the Monte Carlo simulation and their absolute values were averaged over all predictions to represent the contribution of each variable to the prediction. Only the variables with non-zero coefficients are plotted. *** Total observations were randomly assigned to 10 groups. Within each of the 10 iterations, one group was set aside (a test set), and the entire procedure of the two-step elastic net regression was applied to the remaining 9 groups (a training set). Each column represents the results of each iteration. Black cells indicate zero coefficients. Forced = elastic net regression did not identify non-zero coefficient but forced due to their corresponding higher order term(s). Not forced = elastic net regression identified non-zero coefficient.

Table 4

HbA1c z-score changes predicted by the elastic net regression* assuming different environmental scenarios, main model and different sensitivity analyses.

Scenario	All (N = 33'989)	Urban (N = 16'965)	Non- urban (N = 17'024)	Non- smokers (N = 28'089)	Smokers (N = 5'900)
1. Improving air quality	-0.056	-0.011	-#	-0.078	-#
2. Increasing greenness	-#	-#	-#	+0.0015	-#
3. Climate change	+0.012	+0.011	-#	+0.019	-#
4. Improving air quality in the presence of climate change	-0.071	-0.0077	-#	-0.084	-#
5. Increasing greenness in the presence of climate change	+0.012	+0.011	-#	+0.018	-#

* Applied to residuals from a linear mixed effects model of HbA1c z-scores, adjusted for age (linear, quadratic, and cubic terms), sex, smoking status, marital status, employment status, individual education, population density, and cohort. For BAMSE and PIAMA, the model was not adjusted for marital status, employment status, and individual education but for parental education.

No non-zero coefficient was found for any relevant variable.

4.2. Novel evidence for temperature effects in exposome context

We observed strong contributions of temperature variables, either as

main effect (tsd and tsdsq) or in interaction with particulate matter (pm10_tsd and pm25_tav). Exposure to extreme hot or cold air temperatures is associated with short-term increases in diabetes-related morbidity and mortality according to a recent *meta-analysis* of time series and case-crossover studies (Song et al., 2021). Epidemiological studies support heatwave effects on diabetes incidence (Cheng et al., 2019; Yang et al., 2025) and it has been projected that each 1 °C rise in global temperature could lead to at least 100'000 additional new diabetes cases per year worldwide (Meo and Meo, 2024). Acute exposure to high or cold temperature was associated with inflammation-related proteins, which in turn showed association with HbA1c (Yu et al., 2026). Yet the evidence for long-term exposure to hot or cold temperature on T2D incidence and prevalence remains inconsistent (Xi et al., 2026) and the evidence on the associations of heat extremes and climate change with HbA1c in diabetes-free individuals is scarce.

Evidence on independent and cumulative effects of air pollution and temperature in epidemiologic studies applying multipollutant models is very rare (Sørensen et al., 2022; Xi et al., 2026; Yang et al., 2025). Based on data from two follow-up waves of the China Health and Retirement Longitudinal Study (CHARLS) conducted in 2015 and 2018, in adults free of diabetes at baseline, air pollution was found to potentially amplify the association between heatwaves and incident diabetes (Yang et al., 2025). Based on longitudinal data from the German KORA cohort, three phenotype clusters (insulin deficiency; age-related diabetes; insulin-resistance) were derived as endpoints using k-means clustering (Xi et al., 2026). Air pollution and temperature exposure were more consistently associated with age-related diabetes and insulin-resistant diabetes. Multi-pollutant analyses revealed associations of PM_{2.5}, PM_{2.5} absorbance, and PM₁₀ with the likelihood of belonging to the insulin resistant diabetes cluster independent of adjustment for air

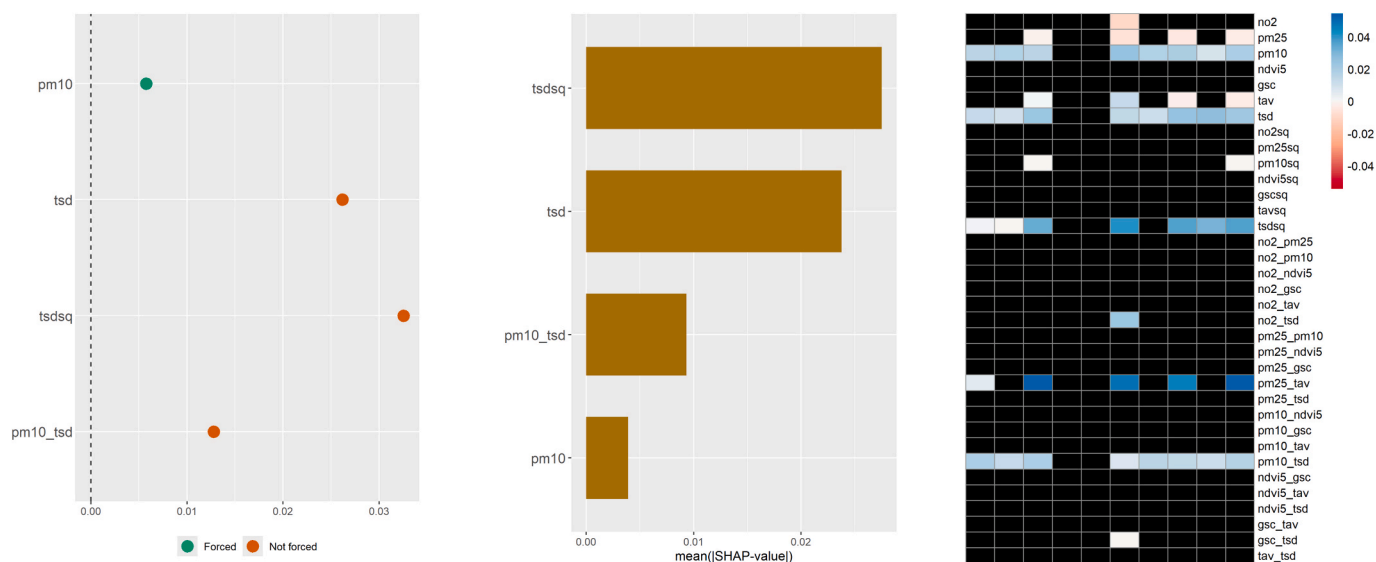


Fig. 4. Non-zero coefficients from elastic net regression of exposome features on HbA1c z-score*, mean absolute SHAP values**, and 10-fold cross-validation results***, restricted to urban areas. Effect estimates by 1 standard deviation change in the corresponding exposure, conditional on all other variables. * Residuals from a linear mixed effects model, adjusted for age (linear, quadratic, and cubic terms), sex, smoking status, marital status, employment status, individual education, population density, and cohort. For BAMSE and PIAMA, the model was not adjusted for marital status, employment status, and individual education, but for parental education instead. ** Approximated SHAP values were calculated based on the Monte Carlo simulation and their absolute values were averaged over all predictions to represent the contribution of each variable to the prediction. Only the variables with non-zero coefficients are plotted. *** Total observations were randomly assigned to 10 groups. Within each of the 10 iterations, one group was set aside (a test set), and the entire procedure of the two-step elastic net regression was applied to the remaining 9 groups (a training set). Each column represents the results of each iteration. Black cells indicate zero coefficients. Forced = elastic net regression did not identify non-zero coefficient but forced due to their corresponding higher order term(s). Not forced = elastic net regression identified non-zero coefficient.

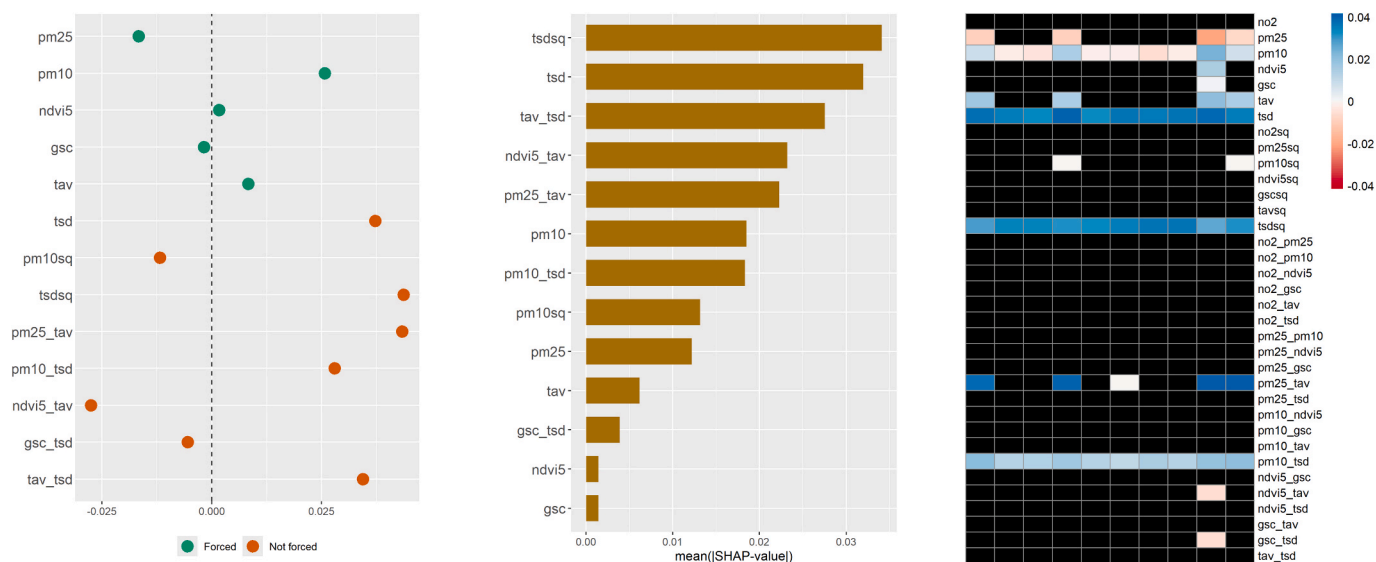


Fig. 5. Non-zero coefficients from elastic net regression of exposome features on HbA1c z-score*, mean absolute SHAP values**, and 10-fold cross-validation results***, restricted to non-smokers. Effect estimates by 1 standard deviation change in the corresponding exposure, conditional on all other variables. * Residuals from a linear mixed effects model, adjusted for age (linear, quadratic, and cubic terms), sex, marital status, employment status, individual education, population density, and cohort. For BAMSE and PIAMA, the model was not adjusted for marital status, employment status, and individual education, but for parental education instead. ** Approximated SHAP values were calculated based on the Monte Carlo simulation and their absolute values were averaged over all predictions to represent the contribution of each variable to the prediction. Only the variables with non-zero coefficients are plotted. *** Total observations were randomly assigned to 10 groups. Within each of the 10 iterations, one group was set aside (a test set), and the entire procedure of the two-step elastic net regression was applied to the remaining 9 groups (a training set). Each column represents the results of each iteration. Black cells indicate zero coefficients. Forced = elastic net regression did not identify non-zero coefficient but forced due to their corresponding higher order term(s). Not forced = elastic net regression identified non-zero coefficient.

temperature. Joint analyses found that PM_{2.5} or PM_{2.5} absorbance in combination with temperature standard deviation increased the odds of being in age-dependent and insulin resistant diabetes clusters. Exposure mixture effects exceeded single exposure model derived effects. The study points to the importance of considering diabetes subtypes in future

exposome studies.

4.3. Associations are restricted in urban areas

The observed associations are largely restricted to the urban

environment. This most likely reflects both higher air pollution levels and heat island intensities in urban environment. When the exposure distribution was stratified by urbanicity as an ad-hoc descriptive analysis (Fig. S9), air pollution was consistently higher in urban than in non-urban areas across cohorts and surveys. Temperature and its variation was slightly higher except in SNAC-K.

Although the current European cross-sectional study findings may not be extrapolated to other areas, it may bear global implications in particular for Asian mega-cities where co-occurrence of high levels of air pollution and urban heat islands is observed. Strong positive correlations between air pollution and temperature was reported in Seoul (Ngarambe et al., 2021) and in Delhi (Das et al., 2025). A long-term study reported decreasing frequency but increasing intensity of co-occurrence of extreme heat and air pollution in Pearl River Delta region including e.g. Guangzhou and Hong Kong (Das et al., 2025).

4.4. Larger benefits of improving air quality in non-smokers

The estimated benefit of a scenario that assumes air quality improvements to likely meet WHO guideline values (WHO, 2021) is predicted to increase in the presence of a parallel temperature change scenario that reflects climate change. The observed pattern, characterized by benefits of improved air quality and increase of such benefit in the presence of climate change, strengthens when restricted to non-smokers, while it disappears in smokers. Smoking-induced inflammation may share the same biological pathways that manifest the effects of environmental hazards such as air pollution on glucose metabolism and therefore mask the effects of these hazards.

4.5. Exposome-HbA1c associations disappeared when stratified by adiposity

The exposome-HbA1c associations were abolished in both normal/underweight and overweight/obese strata. This may be explained by potential mediation of the association by adiposity. A recent Chinese study reported that cumulative exposure to air pollutants were associated with increased risk of insulin resistance, and the association was largely mediated by BMI (Liu et al., 2025).

4.6. Comparison to the previous findings on lung function

In contrast to our previous results for lung function (Jeong et al., 2025), the predicted benefit of improved air quality is estimated to increase in the presence of climate change. This difference may point to different disease pathways. In lung function, climate change may promote certain vegetation types and increase pollen exposure that abolish any beneficial effect of reduction in air pollution from fossil fuel burning and industrial activities. In glycemia, air quality may become more relevant in the context of climate change due to increasing time spent outdoors and exposure to ambient air pollution (e.g. more window opening). It is important to point out that in both cases, the observed interdependence of exposome associations with health outcomes underlines the relevance of health-in-all-policy approaches, such as ambient air quality policies, policies to decrease urban heat islands, or policies to implement heat and air pollution mitigation measures.

Also in contrast to lung function, no interactions of either air pollutants or temperature with greenness or distance to green space were sufficiently strong to be selected. While greenness is hypothesized to have both, beneficial (e.g. promoting physical activity and preventing obesity) and adverse (e.g. allergenic) effects on lung function (Mueller et al., 2022), with the latter potentially being dependent on air quality and temperature, the evidence for T2D points largely to no or a preventive role of greenness (De la Fuente et al., 2021).

4.7. Noise remains a feature to be included in future exposome studies

Several previous large and well conducted studies reported joint effects of environmental exposures, including transportation noise, on diabetes (Yang et al., 2025; Sørensen et al., 2022; Xi et al., 2026; Klompaker et al., 2019; Hu et al., 2023). For example, significant effects of co-exposures to UFP, NO₂, noise, and greenness on T2D incidence were observed in a large Danish cohort, with their cumulative effects being higher than the individual effects (Sørensen et al., 2022). In our sensitivity analysis, adjustment for noise exposure did not alter the associations of air pollutants, greenness, and temperature with HbA1c. But the Danish results argue for including noise in future exposome studies, when pan-European transportation noise maps become available.

4.8. Strengths and limitations

The strengths of our study include: i) large sample size; ii) access to data from well-characterized population-based European cohorts covering adolescence to late adulthood; iii) harmonized pan-European spatio-temporal maps to characterize external exposures at the residential address at fine resolution (de Hoogh et al., 2025); iv) largely harmonized covariate data; and v) analysis of normal glycemia levels from diabetes-free participants, which increases the likelihood that observed associations reflect disease development, not disease control.

There are limitations to our study, which are in common with most multi-cohort exposome studies and cannot be resolved by analytical choices: i) Causal inference is not possible in the light of the cross-sectional and observational study design. ii) The results may be biased due to differential measurement error. Type, likelihood, and magnitude of measurement error vary across exposures. iii) Adjusting for cohort as a proxy for behavioral mediators limited the exposure contrast to within-cohort contrasts. It may to some extent be a form of over-adjustment. iv) Complete case analysis may have introduced bias and therefore limited the generalizability of our findings. v) Cross-sectional design made it impossible to disentangle mediation from confounding. We explored the role of BMI as a mediator by not adjusting for but stratifying by BMI. This left unaddressed its role as a confounder. vi) We cannot rule out residual confounding due to lifestyle factors not adjusted in the model, e.g. diet and physical activity. Adjusting for cohort may have addressed some of these confounders and decreased the risk of residual confounding.

Although our study took advantage of the harmonized European exposure models developed in the EXPANSE project, data availability still limited our study: i) Daily temperature estimates from 2003 were used for blood sampled in 2003 or earlier. We acknowledge that this extrapolation may lead to misclassification error, considering the 2003 heat wave in Europe. To reduce the risk of this error, we decided not to include warm season average of daily maximum temperature and cold season average of daily minimum temperature unlike in Jeong et al (Jeong et al., 2025). ii) The exposome approach was hindered by the unavailability of harmonized European-wide models for transportation noise and by the limitation of NDVI and distance to greenspace in sufficiently characterizing the type and quality of greenspace from a behavioral perspective. iii) Given the fact that temporal availability of exposure maps varied by domain, that temporal variability differs between exposure domains, that latency of health effects likely varies by exposure, and that HbA1c is a semi-acute phenotype reflecting blood glucose levels within approximately 3 months before blood draw, associations may reflect a mixture of semi-acute and chronic exposure effects. A German study of non-diabetic adults explicitly compared different lags (1-, 2-, 3-, 7-, 14-, 45-, 60-, 75-, 105-, 120-, and 182-d means) and reported that 75-105d PM_{2.5} exposure showed the strongest association with HbA1c (Lucht et al., 2018). A Mexican study reported that 3- and 6-month average but not 12-month average was associated with HbA1c for both PM_{2.5} and temperature (He et al., 2022).

Our study cannot differentiate semi-acute and chronic effects.

Several limitations are due to our analytical choice of elastic net regression: i) the difficulty to obtain unbiased standard errors; ii) the non-informative interpretation of the single coefficients in presence of interaction and non-linear terms; iii) the unstable variable selection in case of strong collinearity. We believe, however, the current approach provides useful tools to navigate the health effects of multiple exposome factors and their interactions within and across domains, in particular aided by the environmental scenario approach.

5. Conclusions

Long-term exposure to higher levels of air pollution and temperature variability and their interactions showed associations with HbA1c that are in line with increasing the risk of T2D development in people not yet affected by the disease. The results point towards the relevance of health-in-all-policy perspective.

CRedit authorship contribution statement

A. Jeong: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **J. Edstorp:** Writing – review & editing, Writing – original draft, Validation, Data curation, Conceptualization. **G. Lovison:** Writing – review & editing, Methodology, Conceptualization. **R. Pickford:** Writing – review & editing, Project administration, Conceptualization. **A. Bergström:** Data curation. **N. Blay:** Data curation. **A. Bussalleu:** Writing – review & editing, Data curation. **P. Dadvand:** Data curation. **A. Dalecka:** Writing – review & editing, Validation, Data curation. **M. Imboden:** Project administration, Investigation. **S. Kress:** Writing – review & editing, Validation, Data curation. **Y. Shen:** Writing – review & editing, Data curation. **E. Sochacka-Tatara:** Writing – review & editing, Project administration. **E. Thiering:** Writing – review & editing, Data curation. **B. Thorand:** Writing – review & editing, Methodology, Data curation. **K. Wolf:** Writing – review & editing, Resources, Data curation. **Z. Yu:** Data curation. **R. de Cid:** Funding acquisition, Project administration. **U. Gehring:** Writing – review & editing, Project administration, Funding acquisition, Data curation, Conceptualization. **P. Ljungman:** Writing – review & editing, Project administration, Data curation. **P. Magnusson:** Project administration. **O. Mikeš:** Project administration, Data curation. **A. Pac:** Writing – review & editing, Project administration, Funding acquisition, Data curation. **H. Pikhart:** Writing – review & editing, Project administration, Funding acquisition. **D. Rizzuto:** Writing – review & editing, Project administration, Funding acquisition. **T. Schikowski:** Project administration, Funding acquisition. **M. Standl:** Project administration, Funding acquisition. **K. de Hoogh:** Data curation, Writing – review & editing. **E. Melén:** Writing – review & editing, Project administration, Funding acquisition. **R.C. Vermeulen:** Funding acquisition. **J.J. Vlaanderen:** Project administration, Funding acquisition. **G. Pershagen:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **A. Peters:** Project administration, Funding acquisition, Conceptualization. **N. Probst-Hensch:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Funding acquisition, Conceptualization.

Funding

The EXPANSE project is funded by the European Union's Horizon 2020 research and innovation program (No. 874627). The current work was further supported by the Swedish Research Council (2023–02077). See supplementary document for cohort-specific funding.

Declaration of competing interest

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2026.110538>.

Data availability

Data will be made available on request.

References

- Bailey, M.J., Naik, N.N., Wild, L.E., Patterson, W.B., Alderete, T.L., 2020. Exposure to air pollutants and the gut microbiota: a potential link between exposure, obesity, and type 2 diabetes. *Gut Microbes* 11 (5), 1188–1202.
- Bates, D., Mächler, M., Bolker, B.M., Walker, S.C., 2015. Fitting Linear Mixed-Effects Models using lme4. *J. Stat. Softw.* 67 (1), 1–48.
- Beulens, J.W.J., Pinho, M.G.M., Abreu, T.C., den Braver, N.R., Lam, T.M., Huss, A., et al., 2022. Environmental risk factors of type 2 diabetes-an exposome approach. *Diabetologia* 65 (2), 263–274.
- Brandon, G., 2019. fastshap: Fast Approximate Shapley Values. Contributed Packages, CRAN.
- Brunekreef, B., Strak, M., Chen, J., Andersen, Z.J., Atkinson, R., Bauwelinck, M., et al., 2021. Mortality and Morbidity Effects of Long-Term Exposure to Low-Level PM(2.5), BC, NO(2), and O(3): an Analysis of European Cohorts in the ELAPSE Project. *Res. Rep. Health Eff. Inst.* 2021 (208), 1–127.
- Bussalleu, A., Hoek, G., Kloog, I., Probst-Hensch, N., Rösli, M., de Hoogh, K., 2024. Modelling Europe-wide fine resolution daily ambient temperature for 2003–2020 using machine learning. *Sci. Total Environ.* 928, 172454.
- Chen, S., Cao, Z., Chen, W., Zhao, J., Jiao, L., Prettnner, K., et al., 2026. The global macroeconomic burden of diabetes mellitus. *Nat. Med.* 32 (1), 126–138.
- Cheng, J., Xu, Z., Bambrick, H., Su, H., Tong, S., Hu, W., 2019. Impacts of exposure to ambient temperature on burden of disease: a systematic review of epidemiological evidence. *Int. J. Biometeorol.* 63 (8), 1099–1115.
- Das, M., Das, A., Singha, S., 2025. The heat-pollution paradox: understanding the relationship between land surface temperature and air pollution in a heavily polluted megacity. *Atmos. Pollut. Res.* 16 (8).
- de Hoogh, K., Hoek, G., Flückiger, B., Bussalleu, A., Vienneau, D., Jeong, A., et al., 2025. A Europe-wide characterization of the external exposome: a spatio-temporal analysis. *Environ. Int.* 200, 109542.
- De la Fuente, F., Saldías, M.A., Cubillos, C., Mery, G., Carvajal, D., Bowen, M., et al., 2021. Green Space Exposure Association with Type 2 Diabetes Mellitus, Physical activity, and Obesity: a Systematic Review. *Int. J. Environ. Res. Public Health* 18 (1), 97.
- den Braver Nicole, N.R., Lakerveld, J., Rutters, F., Penninx, B.W., Generaal, E., Visser, M., et al., 2025. Neighborhood Retail Food Environment, Diet Quality and Type 2 Diabetes Incidence in 4 Dutch Cohorts. *J. Nutr.* 155 (7), 2367–2375.
- Friedman, J., Hastie, T., Tibshirani, R., 2010. Regularization Paths for Generalized Linear Models via Coordinate Descent. *J. Stat. Softw.* 33 (1), 1–22.
- Gao, W., Lin, W., Tian, M., Fan, S., Edwards, S., Tran, J., et al., 2025. Ambient Particulate Matter Exposure Impairs Gut Barrier Integrity and Disrupts Goblet Cell Function. *Biomedicines* 13 (8).
- Gong, X., Wang, S., Wang, X., Zhong, S., Yuan, J., Zhong, Y., et al., 2024. Long-term exposure to air pollution and risk of insulin resistance: a systematic review and meta-analysis. *Ecotoxicol. Environ. Saf.* 271, 115909.
- Haw, J.S., Galaviz, K.I., Straus, A.N., Kowalski, A.J., Magee, M.J., Weber, M.B., et al., 2017. Long-term Sustainability of Diabetes Prevention Approaches: a Systematic Review and Meta-analysis of Randomized Clinical Trials. *JAMA Intern. Med.* 177 (12), 1808–1817.
- He, M.Z., Kloog, I., Just, A.C., Gutierrez-Avila, I., Colicino, E., Tellez-Rojo, M.M., et al., 2022. Intermediate- and long-term associations between air pollution and ambient temperature and glycated hemoglobin levels in women of child bearing age. *Environ. Int.* 165.
- Huang, Q., Li, Y., Yu, M., Lv, Z., Lu, F., Xu, N., et al., 2025. Global burden and risk factors of type 2 diabetes mellitus from 1990 to 2021, with forecasts to 2050. *Front. Endocrinol. (Lausanne)*, 16, 1538143.
- Hu, X., Yang, T., Xu, Z., Jin, J., Wang, J., Rao, S., et al., 2023. Mediation of metabolic syndrome in the association between long-term co-exposure to road traffic noise, air pollution and incident type 2 diabetes. *Ecotoxicol. Environ. Saf.* 258, 114992.
- Jeong, A., Lovison, G., Bussalleu, A., Cirach, M., Dadvand, P., de Hoogh, K., et al., 2025. Lung function-associated exposome profile in the era of climate change: Pooled analysis of 8 population-based European cohorts within the EXPANSE project. *Environ. Int.* 196, 109269.
- Klompaker, J.O., Janssen, N.A.H., Bloemasma, L.D., Gehring, U., Wijga, A.H., van den Brink, C., et al., 2019. Associations of combined Exposures to Surrounding Green, Air Pollution, and Road Traffic Noise with Cardiometabolic Diseases. *Environ. Health Perspect.* 127 (8), 87003.
- Liu, P., Zhang, Z., Luo, M., 2025. Relationship between air pollution exposure and insulin resistance in chinese middle-aged and older populations: evidence from chinese cohort. *Front. Public Health* 13, 1551851.

- Liu, X., Peng, G., Lin, Y., Chen, W., Geng, H., Liang, J., 2026. Environmental pollutants associated with blood glucose levels in healthy individuals. *Sci. Rep.*
- Lucht, S.A., Hennig, F., Matthiessen, C., Ohlwein, S., Icks, A., Moebus, S., et al., 2018. Air Pollution and Glucose Metabolism: an Analysis in Non-Diabetic Participants of the Heinz Nixdorf recall Study. *Environ. Health Perspect.* 126 (4), 047001.
- Mackenbach, J.D., Stuber, J.M., Beulens, J.W.J., 2025. Evidence on the effectiveness and equity of population-based policies to reduce the burden of type 2 diabetes: a narrative review. *Diabetologia* 68 (2), 281–294.
- Meo, S.A., Meo, A.S., 2024. Climate Change and Diabetes Mellitus - Emerging Global Public Health Crisis: Observational Analysis. *Pak J Med Sci.* 40 (4), 559–562.
- Mueller, W., Milner, J., Loh, M., Vardoulakis, S., 2022. Wilkinson P. An exploratory systematic review. *Science of the Total Environment*, Exposure to urban greenspace and pathways to respiratory health, p. 829.
- Ngarambe, J., Joen, S.J., Han, C.H., Yun, G.Y., 2021. Exploring the relationship between particulate matter, CO, SO(2), NO(2), O(3) and urban heat island in Seoul. *Korea. J Hazard Mater.* 403, 123615.
- Ohanyan, H., Portengen, L., Kaplani, O., Huss, A., Hoek, G., Beulens, J.W.J., et al., 2022. Associations between the urban exposome and type 2 diabetes: results from penalised regression by least absolute shrinkage and selection operator and random forest models. *Environ. Int.* 170, 107592.
- Parasin, N., Amnuaylojaroen, T., Saokaew, S., Sittichai, N., Tabkhan, N., Dilokthornsakul, P., 2025. Outdoor air pollution exposure and the risk of type 2 diabetes mellitus: a systematic umbrella review and meta-analysis. *Environ. Res.* 269, 120885.
- Shen, Y., de Hoogh, K., Schmitz, O., Clinton, N., Tuxen-Bettman, K., Brandt, J., et al., 2022. Europe-wide air pollution modeling from 2000 to 2019 using geographically weighted regression. *Environ. Int.* 168, 107485.
- Song, X., Jiang, L., Zhang, D., Wang, X., Ma, Y., Hu, Y., et al., 2021. Impact of short-term exposure to extreme temperatures on diabetes mellitus morbidity and mortality? a systematic review and meta-analysis. *Environ. Sci. Pollut. Res. Int.* 28 (41), 58035–58049.
- Strumbelj, E., Kononenko, I., 2014. Explaining prediction models and individual predictions with feature contributions. *Knowl. Inf. Syst.* 41 (3), 647–665.
- Sorensen, M., Poulsen, A.H., Hvidtfeldt, U.A., Brandt, J., Frohn, L.M., Ketzel, M., et al., 2022. Air pollution, road traffic noise and lack of greenness and risk of type 2 diabetes: a multi-exposure prospective study covering Denmark. *Environ. Int.* 170, 107570.
- Team RC. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing.
- Tian, L., Sun, M., Lin, L., Wang, Y., Yu, Y., Duan, J., et al., 2022. Effects of ambient air pollution on glycosylated hemoglobin: a systematic review and meta-analysis. *Environ. Sci. Pollut. Res. Int.* 29 (36), 53954–53966.
- Vlaanderen, J., de Hoogh, K., Hoek, G., Peters, A., Probst-Hensch, N., Scalbert, A., et al., 2021. Developing the building blocks to elucidate the impact of the urban exposome on cardiometabolic-pulmonary disease: the EU EXPANSE project. *Environ. Epidemiol.* 5 (4), e162.
- WHO Guidelines Approved by the Guidelines Review Committee. WHO global air quality guidelines: Particulate matter (PM(25) and PM(10)), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. Geneva: World Health Organization © World Health Organization 2021.; 2021.
- Wild, C.P., 2005. Complementing the genome with an “exposome”: the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol. Biomarkers Prev.* 14 (8), 1847–1850.
- Xi, Y., Breitner-Busch, S., Dong, Q., Wolf, K., Dallavalle, M., Nikolaou, N., et al., 2026. Longitudinal associations of long-term exposure to ambient air pollution, residential greenness, and air temperature with type 2 diabetes subphenotypes: results from the KORA cohort study. *Environ. Int.* 208, 110043.
- Yang, J., Loos, R.J., Powell, J.E., Medland, S.E., Speliotes, E.K., Chasman, D.I., et al., 2012. FTO genotype is associated with phenotypic variability of body mass index. *Nature* 490 (7419), 267–272.
- Yang, W., Lin, Y., Ye, C., Zhang, X., Jiang, X., 2025. The association between heatwave exposure and the risk of incident diabetes in middle-aged and older adults: a cohort study based on CHARLS. *BMC Public Health* 26 (1), 304.
- Yu, Z., Bjorkander, S., Bendes, A., Nobile, F., Zhang, J., Merid, S.K., et al., 2026. Ambient temperature exposure on inflammatory blood proteins-a longitudinal self-sampling survey in young swedish adults. *iScience* 29 (1), 114383.
- Zheng, Y., Ley, S.H., Hu, F.B., 2018. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat. Rev. Endocrinol.* 14 (2), 88–98.