Data S1. ICD codes to ascertain non-accidental deaths

Ontario’s Registrar General Death File is an annual dataset containing information on all deaths registered in Ontario starting on January 1, 1990. Ontario switched from International Classification of Diseases (ICD)-9 classifications to ICD-10 starting in 2000 to code deaths since January 1, 2000. Therefore, we used ICD-9 codes to define non-accidental deaths (001-799) from 1996 to 1999; from 2000 onward, ICD-10 (A00-R99) codes were used to ascertain non-accidental deaths.

Data S2. Hospital discharge abstracts from the Canadian Institute for Health Information

The Canadian Institute for Health Information Discharge Abstract Database [CIHI-DAD] collects data abstracted from patients’ medical charts at discharge by professional, certified medical coders. This database includes up to 25 diagnostic codes related to the hospitalization. For hospitalizations due to diabetes, we considered any diagnosis code. To ascertain incident acute myocardial infarction and stroke, we considered the most responsible diagnosis code.

Data S3. Missingness of exposure and covariates

We excluded participants with missing exposure data at baseline (n=3,643). To avoid losing substantial statistical power, we included participants with missing covariates. We used different approaches to handle the missingness depending on the amount of missing data. For example, we replaced missing values with the most frequent value (the category with the most participants) for marital status, income quintile, physical activity, working status, alcohol consumption. For family income levels, BMI, and smoking status, we created a separate category of missing values.

Data S4. Ascertainment of prevalent cases of diabetes, acute myocardial infarction (AMI), and stroke

To capture that first-ever incidences of mediators during follow-up, we excluded respondents who had previous physician diagnoses of diabetes, AMI, and/or stroke at the time of entry. We determined prior history of these conditions using the same ICD codes, databases, and algorithms that were used to ascertain incident cases (more details can be found in the main text under the “Mediators” section). The presence of the diagnosis of diabetes, AMI, or stroke between 1991 and the survey date was defined as the prevalent cases.

Data S5. Fitting Aalen additive hazards models

We evaluated the associations between the exposure, the outcome, and the mediators using Aalen additive hazards models. Specifically, for the analysis with incidence of diabetes and AMI considered as mediators, we constructed four Aalen additive hazards models: an outcome model associating PM$_{2.5}$ with deaths by adjusting the joint mediator and three mediator models associating PM$_{2.5}$ with incidence of diabetes, incidence of AMI, and the interaction between diabetes and AMI, respectively. The same approach was applied to the analyses with the other two pairs of sequential mediators considered.
Data S6. R code examples of fitting Aalen additive hazards models and calculating direct, indirect effects, and proportion mediated

```r
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### Paper Title: Chronic PM2.5 Exposure Increases Mortality through Pathways of Metabolic and Cardiovascular Disease: Insights from a Large Population-based Mediation Analysis
### Authors: Li Bai, Tarik Benmarhnia, Chen Chen, Jeffrey C. Kwong, Richard T. Burnett, Aaron van Donkelaar, Randall V. Martin, JinHee Kim, Jay S. Kaufman, Hong Chen
### Contact (code): Li Bai (li.bai@ices.on.ca) and Hong Chen (hong.chen@hc-sc.gc.ca)
### Description: R code example of fitting Aalen additive hazards models and calculating direct, indirect effects, and proportion mediated. This example is for investigating the extent to which the effect of PM2.5 on deaths is mediated by its effect on the development of diabetes and acute myocardial infarction (AMI).
### Required Packages: timereg
### Requires data in counting process format.
### Variable description:
### event: non-accidental deaths (binary)
### PM25: long-term exposure to PM2.5 (continuous)
### m_td: joint mediator indicator (categorical: 1: free of both diabetes and AMI diagnoses during follow-up, 2: developed diabetes only, 3: developed AMI only, and 4: developed both diabetes and AMI)
### M_td1_2: incident diabetes (binary)
### M_td1_3: incident AMI (binary)
### M_td1_4: incident diabetes and AMI (whichever came first) (binary)
### start: start time of follow up in days
### stop: end time of follow up in days (ended when reaching Dec 31, 2017, becoming ineligible for provincial health insurance, or death)
### stop_m1: end time of follow up for diabetes in days (ended when reaching Dec 31, 2017, becoming ineligible for provincial health insurance, death, or receiving the diagnosis of diabetes)
### stop_m2: end time of follow up for AMI in days (ended when reaching Dec 31, 2017, becoming ineligible for provincial health insurance, death, or receiving the diagnosis of AMI)
### cov1: selected categorial covariates such as BMI and smoking
### cov2: selected continuous covariates such as area-level risk factors (e.g., % of low education)
```
library(timereg)

load('... /data/dataset')

m.outcome<-aalen(Surv(start, stop, event)~ const(PM25) + const(factor(m_td)) + const(factor(cov1)) + const(cov2), data=dataset, robust=0, n.sim = 500)

theta1<-m.outcome$gamma[1]
theta1.se<-sqrt(m.outcome$var.gamma[1,1])

theta2_1<-m.outcome$gamma[2]
theta2_1.se=sqrt(m.outcome$var.gamma[2,2])

theta2_2<-m.outcome$gamma[3]
theta2_2.se<-sqrt(m.outcome$var.gamma[3,3])

theta2_3<-m.outcome$gamma[4]
theta2_3.se<-sqrt(m.outcome$var.gamma[4,4])

m.mediator1<-aalen(Surv(start, stop_m1, M_td1_2)~const(PM25) + const(factor(cov1)) + const(cov2), data=data, robust=0, n.sim = 500)

beta1_1 <- m.mediator1$gamma[1]
beta1_1.se <- sqrt(m.mediator1$var.gamma[1,1])

m.mediator2<-aalen(Surv(start, stop_m2, M_td1_3)~const(PM25) + const(factor(cov1)) + const(cov2), data=dat_boot, robust=0, n.sim = 500)

beta1_2<-m.mediator2$gamma[1]
beta1_2.se <-sqrt(m.mediator2$var.gamma[1,1])

m.mediator3<-aalen(Surv(start, stop_m2, M_td1_4)~const(PM25) + const(factor(cov1)) + const(cov2), data=dat_boot, robust=0, n.sim = 500)

beta1_3<-m.mediator3$gamma[1]
beta1_3.se<-sqrt(m.mediator3$var.gamma[1,1])
### rescale the effects

days <- 3796  # mean follow up days of the cohort
pm_unit <- 10  # every 10 unit increase in PM2.5

theta1 <- theta1 * days * pm_unit
theta2_1 <- theta2_1 * days
theta2_2 <- theta2_2 * days
theta2_3 <- theta2_3 * days

beta1_1 <- beta1_1 * days * pm_unit
beta1_2 <- beta1_2 * days * pm_unit
beta1_3 <- beta1_3 * days * pm_unit

### estimate direct, indirect, total effects, and proportion mediated

# natural direct effect
NDE <- theta1
# indirect effect via incident diabetes
NIE1 <- beta1_1 * theta2_1
# indirect effect via incident AMI
NIE2 <- beta1_2 * theta2_2
# indirect effect via the interaction between diabetes and AMI
NIE3 <- beta1_3 * theta2_3
# total indirect effect
NIE.T <- NIE1 + NIE2 + NIE3
# total effect
TE <- NDE + NIE1 + NIE2 + NIE3

# proportion of direct effect
prop_NDE <- NDE / TE
# proportion of indirect effect via incident diabetes
prop_NIE1 <- NIE1 / TE
# proportion of indirect effect via incident AMI
prop_NIE2 <- NIE2 / TE
# proportion of indirect effect via the interaction between diabetes and AMI
prop_NIE3 <- NIE3 / TE
# proportion of total indirect effect
prop_NIE.T <- NIE.T / TE

###end
Table S1. The time period of data collection for each cycle

| Cycle                        | The time period of data collection                  |
|-------------------------------|----------------------------------------------------|
| 1996/1997 cycle of National Population Health Survey | June 1996 - August 1997                           |
| Canadian Community Health Surveys |                                     |
| 2000/2001 cycle               | September 2000 - November 2001                    |
| 2003 cycle                    | January 2003 - November 2003                      |
| 2005 cycle                    | January 2005 - December 2005                      |
| 2007/2008 cycle               | January 2007 - December 2008                      |
| 2009/2010 cycle               | January 2009 - December 2010                      |
| 2011/2012 cycle               | January 2011 - December 2012                      |
| 2013/2014 cycle               | January 2013 - December 2014                      |
| Variable                  | Timing                                         | Level                | Data source                                                                 |
|--------------------------|-----------------------------------------------|----------------------|----------------------------------------------------------------------------|
| **Exposure**             |                                               |                      |                                                                            |
| PM2.5                    | 1995 to the end of follow-up                  | Postal code level†   | Annual estimates of ground-level PM2.5 concentrations developed by van Donkelaar et al. (2019) |
| **Outcome and mediators**|                                               |                      |                                                                            |
| Non-accidental deaths    | from the baseline to the end of follow-up‡    | Individual level     | Office of the Registrar General Vital Statistics Death Database (ORGD)     |
| Incident diabetes        | from the baseline to the end of follow-up     | Individual level     | Hospital discharge abstracts from the Canadian Institute for Health Information, physician service claims from the Ontario Health Insurance Plan database and claims for prescription drugs from the Ontario Drug Benefit database |
| Incident AMI             | from the baseline to the end of follow-up     | Individual level     | Hospital discharge abstracts from the Canadian Institute for Health Information |
| Incident stroke          | from the baseline to the end of follow-up     | Individual level     | Hospital discharge abstracts from the Canadian Institute for Health Information, physician service claims from the Ontario Health Insurance Plan database |
| Incident cardiovascular events | from the baseline to the end of follow-up   | Individual level     | Hospital discharge abstracts from the Canadian Institute for Health Information, physician service claims from the Ontario Health Insurance Plan database |
| **Risk factors**         |                                               |                      |                                                                            |
| Age                      | at baseline                                   | Individual level     | The 1996/1997 cycle of National Population Health Survey (NPHS); the 2000/2001, 2003, 2005, 2007/2008, 2009/2010, 2011/2012, and 2013/2014 cycles of the Canadian Community Health Surveys (CCHS) |
| Sex                      | at baseline                                   | Individual level     |                                                                            |
| Marital status           | at baseline                                   | Individual level (self-reported) |                                                                            |
| White or non-white ethnicity | at baseline                               | Individual level (self-reported) |                                                                            |
| Immigrants or non-immigrants | at baseline                               | Individual level (self-reported) |                                                                            |
| Education                | at baseline                                   | Individual level (self-reported) |                                                                            |
| Household income adequacy| at baseline                                   | Individual level (self-reported) |                                                                            |
| Smoking status           | at baseline                                   | Individual level (self-reported) |                                                                            |
| Smoking pack years (only available in CCHS) | at baseline                               | Individual level (self-reported) |                                                                            |
| Type of drinker                                                                 | at baseline | Individual level (self-reported) |
|--------------------------------------------------------------------------------|-------------|----------------------------------|
| Body mass index (BMI)                                                          | at baseline | Individual level (self-reported)  |
| Physical activity (based on energy expenditure)                                | at baseline | Individual level (self-reported)  |
| Nearest Census based neighbourhood % of recent immigrants                      | in 1996, 2001, 2006, and 2016 | Census Division level\(\) Canadian Census data |
| Nearest Census based neighbourhood % of population aged ≥15 years who had not completed high school | in 1996, 2001, 2006, and 2016 | Census Division level |
| Nearest Census based neighbourhood unemployment rate                            | in 1996, 2001, 2006, and 2016 | Census Division level |
| Nearest Census based neighbourhood income quintile                              | in 1996, 2001, 2006, and 2016 | Census Division level |
| Rural residence (the community size is <= 10,000)                              | from the baseline to the end of follow-up | Postal code level |
| Northern or Southern Ontario                                                   | from the baseline to the end of follow-up | Postal code level |

*These datasets were linked using unique encoded identifiers and analyzed at ICES.
\(\) A single six-digit residential postal code can correspond to one side of a city street between consecutive intersections or a community mailbox or an apartment/business building. Using the Postal Code Conversion File (PCCF), six-character postal codes can be lined to standard Census geographic areas (e.g., dissemination areas, census tracts).
\(\) Eligible respondents were followed up from the time of survey (baseline) and censored when reaching the end of follow-up (December 31, 2017), becoming ineligible for provincial health insurance, or death.
\(\) Census divisions are provincially legislated areas (equivalent to counties).
| Characteristics                                                                 | Diabetes-AMI cohort | Diabetes-stroke cohort |
|--------------------------------------------------------------------------------|---------------------|------------------------|
|                                                                              | All participants | Participants who were diagnosed with diabetes during follow-up | Participants who were diagnosed with AMI during follow-up | Participants who died due to non-accidental causes during follow-up | All participants | Participants who were diagnosed with diabetes during follow-up | Participants who were diagnosed with stroke during follow-up | Participants who died due to non-accidental causes during follow-up |
| N                                                                              | 192,362            | 18,739                 | 4,014                  | 21,318                   | 190,052          | 18,444                 | 8,608                 | 20,258                   |
| PM2.5 exposure at entry [Mean ± SD]                                           | 8.46 ± 2.47        | 8.70 ± 2.68            | 8.59 ± 2.75            | 8.71 ± 2.78              | 8.45 ± 2.47      | 8.69 ± 2.68            | 8.69 ± 2.76            | 8.70 ± 2.78              |
| Individual-level risk factors [Mean ± SD or percent]                          |                    |                        |                        |                          |                  |                        |                        |                          |
| Age at entry (years)                                                          | 49.7 ± 17.5        | 55.5 ± 14.6            | 63.7 ± 14.5            | 70.0 ± 12.8              | 49.4 ± 17.4      | 55.2 ± 14.4            | 66.1 ± 13.9            | 69.7 ± 12.9              |
| Males                                                                         | 44.7               | 48.9                   | 57.7                   | 45.7                     | 45.0             | 49.4                   | 44.4                   | 46.6                     |
| Immigrants                                                                    | 20.3               | 25.0                   | 22.1                   | 22.6                     | 20.2             | 24.9                   | 23.4                   | 22.6                     |
| Nonwhite                                                                       | 11.2               | 12.7                   | 5.7                    | 4.2                      | 11.3             | 12.8                   | 5.7                    | 4.2                      |
| Living in an urban area                                                       | 74.0               | 74.0                   | 70.7                   | 72.4                     | 74.0             | 73.8                   | 73.7                   | 72.4                     |
| Living in southern region                                                      | 86.3               | 85.0                   | 81.8                   | 84.7                     | 86.3             | 84.7                   | 85.0                   | 84.5                     |
| Marital status                                                                |                    |                        |                        |                          |                  |                        |                        |                          |
| Married or common law                                                         | 59.4               | 61.4                   | 56.8                   | 48.4                     | 59.6             | 61.8                   | 54.8                   | 48.6                     |
| Single (never married)                                                        | 19.1               | 12.9                   | 9.3                    | 8.4                      | 19.2             | 12.8                   | 8.1                    | 8.5                      |
| Separate, widowed, or divorced                                                | 21.5               | 25.7                   | 33.9                   | 43.2                     | 21.2             | 25.4                   | 37.1                   | 42.9                     |
| Education                                                                     |                    |                        |                        |                          |                  |                        |                        |                          |
| Less than high school                                                         | 16.6               | 25.4                   | 33.6                   | 38.0                     | 16.4             | 25.3                   | 31.9                   | 38.0                     |
| High school graduation                                                        | 19.5               | 19.1                   | 18.6                   | 18.3                     | 19.5             | 19.1                   | 17.9                   | 18.2                     |
| Some form of postsecondary education                                           | 8.0                | 8.3                    | 7.6                    | 7.3                      | 8.0              | 8.4                    | 7.6                    | 7.4                      |
| Postsecondary graduation                                                      | 56.0               | 47.2                   | 40.2                   | 36.4                     | 56.1             | 47.3                   | 42.6                   | 36.5                     |
| Family income                                                                 |                    |                        |                        |                          |                  |                        |                        |                          |
| ≤$29999                                                                       | 20.4               | 27.3                   | 33.3                   | 41.4                     | 20.1             | 26.7                   | 33.6                   | 40.9                     |
| $30,000-$79,999                                                               | 43.2               | 44.3                   | 40.2                   | 37.1                     | 43.2             | 44.5                   | 41.1                   | 37.4                     |
| ≥$80,000                                                                      | 29.3               | 19.2                   | 15.8                   | 8.8                      | 29.6             | 19.6                   | 13.9                   | 9.1                      |
| Missing                                                                       | 7.1                | 9.2                    | 10.7                   | 12.7                     | 7.1              | 9.2                    | 11.4                   | 12.5                     |
| Smoking (in NPHS)                                                             |                    |                        |                        |                          |                  |                        |                        |                          |
| Never smoker                                                                  | 40.6               | 37.6                   | 33.6                   | 35.2                     | 40.5             | 37.0                   | 41.5                   | 24.9                     |
| Daily smoker          | 24.9 | 24.9 | 30.1 | 24.5 | 24.9 | 24.8 | 19.7 | 31.8 |
|----------------------|------|------|------|------|------|------|------|------|
| Occasional smoker    | 2.0  | 1.8  | 1.1  | 1.7  | 2.0  | 2.0  | 1.7  | 1.7  |
| Always occasional smoker | 1.5  | 1.5  | 0.9  | 1.0  | 1.5  | 1.6  | 0.8  | 1.0  |
| Former daily smoker  | 24.3 | 28.7 | 28.9 | 31.9 | 24.2 | 29.0 | 30.7 | 5.5  |
| Former occasional smoker | 6.8  | 5.6  | 5.4  | 5.6  | 6.8  | 5.6  | 5.5  | 35.1 |

## Smoking (in CCHS)

| Never smoker          | 33.9 | 30.6 | 24.7 | 27.0 | 33.8 | 30.2 | 30.6 | 26.6 |
| Current smoker of <10 pack-years | 8.3  | 4.7  | 2.9  | 2.1  | 8.4  | 4.8  | 2.6  | 2.1  |
| Current smoker of 10-20 pack-years | 5.1  | 4.5  | 5.6  | 3.4  | 5.1  | 4.6  | 3.9  | 3.5  |
| Current smoker of ≥20 pack years | 9.2  | 12.9 | 19.1 | 17.2 | 9.2  | 13.1 | 12.6 | 17.3 |
| Current smoker with missing pack-years | 0.0  | 1.0  | 1.0  | 0.9  | 1.0  | 1.0  | 1.2  | 1.2  |
| Former Smoker who quitted within 5 years | 6.8  | 7.4  | 6.1  | 6.5  | 6.9  | 7.7  | 4.8  | 6.6  |
| Former Smoker who quitted > 5 years | 22.5 | 27.9 | 31.3 | 33.5 | 22.4 | 27.7 | 33.3 | 33.6 |
| Missing               | 13.3 | 11.0 | 9.4  | 9.1  | 13.3 | 11.0 | 11.1 | 9.0  |

## BMI (kg/m2)

| <18.5 | 2.1  | 0.6  | 1.3  | 3.3  | 2.0  | 0.6  | 2.0  | 3.2  |
| 18.5-25.0 | 42.9 | 19.0 | 33.7 | 37.3 | 42.9 | 18.7 | 36.7 | 37.2 |
| 25.0-30.0 | 33.9 | 36.7 | 36.3 | 29.0 | 33.9 | 36.7 | 33.5 | 29.2 |
| 30.0-35.0 | 11.9 | 23.6 | 13.5 | 10.1 | 11.9 | 23.9 | 11.4 | 10.2 |
| ≥35.0 | 4.3  | 12.6 | 4.0  | 3.7  | 4.3  | 12.7 | 3.6  | 3.8  |
| Missing | 4.9  | 7.5  | 11.3 | 16.7 | 4.8  | 7.4  | 12.8 | 16.5 |

## Physical activity

| Active | 24.3 | 18.0 | 18.7 | 15.5 | 24.5 | 18.2 | 19.5 | 16.0 |
| Moderate active | 25.5 | 22.9 | 24.0 | 20.0 | 25.6 | 23.0 | 23.5 | 20.3 |
| Inactive | 50.1 | 59.1 | 57.3 | 64.6 | 50.0 | 58.8 | 57.0 | 63.7 |

### Area-level risk factor* [Mean ± SD or percent]

| Percentage of recent immigrants | 2.6 ± 2.9 | 2.6 ± 3.0 | 2.0 ± 2.6 | 2.2 ± 2.7 | 2.6 ± 2.9 | 2.5 ± 3.0 | 2.2 ± 2.7 | 2.2 ± 2.7 |
| Percentage of the population ≥15 years of age without employment | 7.0 ± 1.4 | 7.0 ± 1.4 | 7.1 ± 1.5 | 7.0 ± 1.4 | 7.0 ± 1.4 | 7.0 ± 1.4 | 7.1 ± 1.4 | 7.0 ± 1.4 |
| Percentage of the population ≥15 years of age with less than a high school education | 26.8 ± 4.4 | 26.8 ± 4.4 | 27.5 ± 4.1 | 27.2 ± 4.1 | 26.8 ± 4.4 | 26.8 ± 4.3 | 27.2 ± 4.1 | 27.3 ± 4.1 |
| Income quintiles | Lowest | 18.4 | 22.0 | 22.9 | 24.7 | 18.4 | 21.9 | 22.5 | 24.7 |
| Level    | 19.7 | 21.1 | 21.6 | 21.3 | 19.6 | 21.0 | 20.7 | 21.3 |
|----------|------|------|------|------|------|------|------|------|
| Lower    | 19.8 | 20.5 | 19.3 | 19.3 | 19.8 | 20.6 | 19.7 | 19.2 |
| Middle   | 22.1 | 19.7 | 19.6 | 18.4 | 22.2 | 19.8 | 19.2 | 18.5 |
| Upper    | 20.0 | 16.6 | 16.7 | 16.3 | 20.0 | 16.7 | 17.9 | 16.3 |
| Uppermost|      |      |      |      |      |      |      |      |

AMI: acute myocardial infarction; BMI: body mass index; CCHS: Canadian Community Health Surveys; NPHS: National Population Health Survey; SD: standard deviation.

* From Canadian Census 2001, at the dissemination area level.
### Table S4. Proportions (%) of the direct and indirect effects derived from the sensitivity analysis

| Path-specific effect | Main analysis * | Sensitivity analysis | Sensitivity analysis | Sensitivity analysis | Sensitivity analysis | Sensitivity analysis | Using a method of dynamic path analysis ‡ |
|----------------------|-----------------|----------------------|----------------------|----------------------|----------------------|----------------------|-------------------------------------|
|                      | Main analysis * | Using the restricted cubic splines of age † | Further adjusting for a linear term for time † | Further adjusting for alcohol consumption † | Further working status † | Further adjusting for sense of belonging to local community † |                      |
| Path-specific effect | Direct effect$\text{§}$ | 81.4 | 83.1 | 84.8 | 82.4 | 78.7 | 82.3 | 77.0 |
| Path-specific effect | Total indirect effect $\text{‖}$ | 18.6 | 16.9 | 15.2 | 17.6 | 21.3 | 17.7 | 23.0 |
| Path-specific effect | Indirect effect via diabetes $\text{§}$ | 4.2 | 2.6 | 1.6 | 3.9 | 5.7 | 4.1 | 2.0 |
| Path-specific effect | Indirect effect via AMI $\text{**}$ | 11.5 | 10.8 | 10.4 | 10.9 | 12.3 | 10.8 | 15.1 |
| Path-specific effect | Indirect effect via the interaction between diabetes and AMI $\text{††}$ | 2.9 | 3.6 | 3.3 | 2.8 | 3.4 | 2.8 | 3.2 |
| Mediators: Incidence of diabetes and stroke | Direct effect | 76.0 | 78.5 | 78.4 | 76.8 | 73.7 | 77.0 | 70.6 |
| Mediators: Incidence of diabetes and stroke | Total indirect effect | 24.0 | 21.5 | 21.6 | 23.2 | 26.3 | 23.0 | 29.4 |
| Mediators: Incidence of diabetes and stroke | Indirect effect via diabetes | 5.3 | 3.6 | 2.3 | 4.7 | 6.9 | 4.9 | 5.4 |
| Mediators: Incidence of diabetes and stroke | Indirect effect via stroke | 13.9 | 15.4 | 16.7 | 13.9 | 13.5 | 13.5 | 18.6 |
| Mediators: Incidence of diabetes and stroke | Indirect effect via the interaction between diabetes and stroke | 4.8 | 2.5 | 2.6 | 4.6 | 5.8 | 4.6 | 5.4 |
| Mediators: Incidence of diabetes and cardiovascular events $\text{‡‡}$ | Direct effect | 68.3 | 70.5 | 70.9 | 69.8 | 65.8 | 69.9 | 61.7 |
| Mediators: Incidence of diabetes and cardiovascular events $\text{‡‡}$ | Total indirect effect | 31.7 | 29.5 | 29.1 | 30.2 | 34.2 | 30.1 | 38.3 |
| Mediators: Incidence of diabetes and cardiovascular events $\text{‡‡}$ | Indirect effect via diabetes | 4.5 | 2.9 | 1.8 | 3.9 | 5.7 | 4.1 | 2.1 |
| Mediators: Incidence of diabetes and cardiovascular events $\text{‡‡}$ | Indirect effect via cardiovascular events | 22.8 | 23.9 | 24.6 | 22.1 | 23.4 | 21.8 | 31.5 |
| Mediators: Incidence of diabetes and cardiovascular events $\text{‡‡}$ | Indirect effect via the interaction between diabetes and cardiovascular events | 4.5 | 2.7 | 2.7 | 4.1 | 5.0 | 4.2 | 4.7 |

AMI: acute myocardial infarction; BMI: body mass index.

* Results from the main analysis were presented in Table 2.
† Aalen additive hazards models adjusted for the selected individual-level covariates measured at baseline (i.e., age, sex, marital status, education, immigration status, household income adequacy, smoking status, smoking pack years, type of drinker, daily consumption of total fruits and vegetables, physical activity, and BMI) and time-varying area-level variables (i.e., education, income, % of unemployment, % of immigrants, indicators for rural/urban and north/south).
These effects were estimated using a method of dynamic path analysis (Aalen et al., 2019). This approach estimates cumulative direct and indirect effects of PM$_{2.5}$ on non-accidental deaths over follow-up based on the additive hazards model and a sequential linear model for the mediator process. We were unable to perform bootstrapping to derive confidence intervals for the point estimates because of the computational challenges.

§The effect of PM$_{2.5}$ on non-accidental deaths not mediated by selected mediators.
‖The total effect of PM$_{2.5}$ on non-accidental deaths mediated by selected mediators.
#The effect mediated through the first mediator alone.
**The effect mediated through the second mediator alone.
††The effect mediated through the interaction between the two mediators.
‡‡A composite indicator of incident AMI and stroke (whichever occurred first).
|                                      | The DM-CVD cohort† | The cohort with prevalence cases added back |
|--------------------------------------|--------------------|---------------------------------------------|
|                                      | 1.79               | 2.26                                        |
| Rate difference (per 1,000 person-years) | 0.93-2.65          | 1.33-3.20                                  |
| 95% CI                               |                    |                                              |
| Hazard ratio                         | 1.16               | 1.17                                        |
| 95% CI                               | 1.08-1.25          | 1.09-1.26                                  |

AMI: acute myocardial infarction; CVD: cardiovascular events (AMI or stroke); PM2.5: fine particulate matter.

*per 10 μg/m³ increase.
†Excluding people who had prior diagnosis of diabetes and cardiovascular events (AMI or stroke).
Figure S1. The total effect of exposure to fine particulate matter (PM$_{2.5}$) on non-accidental all-cause deaths which is estimated as the sum of the direct effect and indirect effects through mediators.