This item is the archived peer-reviewed author-version of:

Air pollution and ST-elevation myocardial infarction: A case-crossover study of the Belgian STEMI registry 2009-2013

Reference:

Argacha J. F., Collart P., Wauters A., Kayaert P., Lochy S., Schoors D., Sonck J., de Vos T., Forton M., Brasseur O.,- Air pollution and ST-elevation myocardial infarction: A case-crossover study of the Belgian STEMI registry 2009-2013
International journal of cardiology - ISSN 0167-5273 - 223(2016), p. 300-305
Full text (Publisher's DOI): <https://doi.org/10.1016/J.IJCARD.2016.07.191>
To cite this reference: <https://hdl.handle.net/10067/1382440151162165141>

Accepted Manuscript

Air pollution and ST-elevation myocardial infarction: A case-crossover study of the Belgian STEMI registry 2009–2013

J.F. Argacha, P. Collart, A. Wauters, P. Kayaert, S. Lochy, D. Schoors, J. Sonck, T. de Vos, M. Forton, O. Brasseur, C. Beauloye, S. Gevaert, P. Evrard, Y. Coppieters, P. Sinnaeve, M.J. Claeys

PII: S0167-5273(16)31583-2
DOI: doi: [10.1016/j.ijcard.2016.07.191](https://doi.org/10.1016/j.ijcard.2016.07.191)
Reference: IJCA 23158

To appear in: *International Journal of Cardiology*

Received date: 31 May 2016
Accepted date: 28 July 2016

Please cite this article as: Argacha JF, Collart P, Wauters A, Kayaert P, Lochy S, Schoors D, Sonck J, de Vos T, Forton M, Brasseur O, Beauloye C, Gevaert S, Evrard P, Coppieters Y, Sinnaeve P, Claeys MJ, Air pollution and ST-elevation myocardial infarction: A case-crossover study of the Belgian STEMI registry 2009–2013, *International Journal of Cardiology* (2016), doi: [10.1016/j.ijcard.2016.07.191](https://doi.org/10.1016/j.ijcard.2016.07.191)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Air pollution and ST-elevation myocardial infarction:**A case-crossover study of the Belgian STEMI registry 2009-2013****Short title: *Air pollution and STEMI***

J.F. Argacha^{1*}, P. Collart^{2*}, A. Wauters³, P. Kayaert¹, S. Lochy¹, D. Schoors¹, J. Sonck¹, T. de Vos⁴, M. Forton⁴, O. Brasseur⁴, C. Beauloye⁵, S. Gevaert⁶, P. Evrard⁷, Y. Coppieters², P. Sinnaeve⁸ and M.J. Claeys⁹

- 1) Cardiology Department, Universitair Ziekenhuis Brussel, VUB, Belgium
- 2) Research center in Epidemiology, biostatistics and clinical research, School of Public Health, Université libre de Bruxelles (ULB), Belgium
- 3) Cardiology Department, Erasme Hospital, ULB, Belgium
- 4) Laboratory of Environmental Research, Brussels Environment, Brussels, Belgium
- 5) Division of Cardiology, Cliniques Universitaires Saint Luc Hospital and Pole de Recherche Cardiovasculaire, Institut de Recherche Expérimentale et Clinique, Brussels, Belgium
- 6) Cardiology Department, Ghent University Hospital, Gent, Belgium
- 7) Cardiology Department, Mont Godine Hospital, UCL, Belgium
- 8) Cardiology Department, Universitair Ziekenhuis Leuven, KUL, Belgium
- 9) Cardiology Department, Universitair Ziekenhuis Antwerpen, UA, Belgium

*: Both first authors contributed equally to this study.

Address for correspondence:

Jean François Argacha, Department of Cardiology, Universitair Ziekenhuis Brussel
Laarbeeklaan 101, 1060 Jette, Belgium.

E-mail: jean-francois.argacha@uzbrussel.be, Phone: +32-2-476 34 88.

Acknowledgements:

Authors are indebted to all the physicians and nurses involved in the BIWAC registry. The authors thank Yves Thorrez for his generous technical support.

Funding sources:

The National ST-segment Elevation Myocardial Infarction Database is financially supported by a grant from the Ministry of Social Affairs of the Belgium government.

Disclosure of conflicts of interest: The authors declare no competing financial interests.

ABSTRACT

Background: Previous studies have shown that air pollution particulate matter (PM) is associated with an increased risk for myocardial infarction. The effects of air pollution on the risk of ST-elevation myocardial infarction (STEMI), in particular the role of gaseous air pollutants such as NO₂ and O₃ and the susceptibility of specific populations, are still under debate.

Methods: All patients entered in the Belgian prospective STEMI registry between 2009 and 2013 were included. Based on a validated spatial interpolation model from the Belgian Environment Agency, a national index was used to address the background level of air pollution exposure of Belgian population. A time-stratified and temperature-matched case-crossover analysis of the risk of STEMI was performed.

Results: A total of 11428 STEMI patients were included in the study. Each 10 µg/m³ increase in PM₁₀, PM_{2.5} and NO₂ was associated with an increased odds ratio (OR) of STEMI of 1.026 (CI_{95%}: 1.005-1.048), 1.028 (CI_{95%}: 1.003-1.054) and 1.051 (CI_{95%}: 1.018-1.084), respectively. No effect of O₃ was found. STEMI was associated with PM₁₀ exposure in patients ≥75 y.o. (OR: 1.046, CI_{95%}: 1.002-1.092) and with NO₂ in patients ≤54 y.o. (OR: 1.071, CI_{95%}: 1.010-1.136). No effect of air pollution on cardiac arrest or in-hospital STEMI mortality was found.

Conclusion: PM_{2.5} and NO₂ exposure incrementally increase the risk of STEMI. The risk related to PM appears to be greater in the elderly, while younger patients appear to be more susceptible to NO₂ exposure.

INTRODUCTION

Ambient air pollution is a mixture of particulate matter (PM) and gaseous pollutants such as sulphur dioxide, nitric dioxide (NO₂) and ozone (O₃). PM_{2.5} have an aerodynamic diameter <2.5 µm, while PM₁₀ have an aerodynamic diameter <10 µm. PM_{2.5} and NO₂ predominantly originate from the combustion of fossil fuels, including industrial activities or vehicles, whereas PM₁₀ also originates from natural processes[1].

The first health consequences of industrial smog were described in Belgium in 1930 after the infamous Meuse Valley fog incident, which caused 60 deaths[2]. Today, air pollution is recognized by the World Health Organization (WHO) as a major cause of avoidable death[3] and is responsible for an estimated life expectancy reduction of approximately 6 months per 10 µg/m³ increment of PM₁₀[4]. In addition to the pulmonary and carcinogenic effects of air pollution, exposition to air pollution has been associated with an increased risk of cardiovascular events and death[5]. A recent meta-analysis showed that a 10 µg/m³ increase in PM₁₀ increased coronary events by 12%[6]. A similar increase in acute coronary syndrome (ACS) is observed with 5 µg/m³ increases in PM_{2.5}, suggesting that fine particulate matter has even more pronounced cardiovascular toxicity[6]. Due to the risk size and the large proportion of the population that is exposed, particulate air pollution and traffic exposure may be an important trigger of myocardial infarction in densely polluted areas. In addition to air particles, the role of gaseous air pollutant remains controversial, with an inconsistent relationship found between myocardial infarction and exposure to O₃ and NO₂[7],[8].

Despite numerous in vitro and in vivo interventional studies showing an acute effect of pollutants on the general pathophysiological determinants of ACS[9], the influence of air pollution on the particular subset of STEMI patients has not yet been established because most studies, that have focused on the relationship between air pollution and ACS, did not stratify according to infarction type[7][10][11]. In addition, whether air pollution-related

STEMI risk is uniform across the whole population or whether certain subpopulations (e.g., the elderly or diabetics) are more susceptible remains unclear. Air pollution exposure may trigger STEMI in a subset of patients with accelerated arteriosclerosis, as is the case in diabetic or hypertensive patients and in patients with previous documented coronary artery disease[8][12][13].

To address these issues, we studied the association between short-term exposure to PM₁₀, PM_{2.5}, O₃, NO₂ and hospitalization for STEMI at a comprehensive national level. In addition, we set out to determine which comorbidities might exacerbate this risk. Finally, we evaluated whether patients presenting with a STEMI in the setting of short-term air pollution exposure have an increased mortality risk. The association between a national index of background air pollution, which Belgium population is exposed to, and the onset of STEMI in the following 24 h of the exposure was studied by a time-stratified case-crossover design. In a previous work on such statistical design[11], we demonstrated that above the different possible referent selection strategies in case-crossover design[14], the time-stratified and temperature-matched is particularly interesting to ensure a control of the very well known confounding effect of air temperature on the risk of acute myocardial infarction[15,16].

MATERIAL AND METHODS

Study population and data source

The Belgian STEMI registry is a prospective observational registry of unselected Belgian STEMI patients presenting to 72 Belgian hospitals within 24 h of symptom onset. The rationale and design of this nationwide compulsory registry has been described previously[17][18]. In addition to clinical and procedural variables, in-hospital mortality is also recorded. The registry is an initiative of the Belgian Working Group on Acute Cardiology (BIWAC) and is supported by the Belgian government and the Belgian Society of Cardiology. Data are electronically collected in a central web based eCRF, and the database is managed by an independent electronic data capture provider (Lambda Plus, SA, Gembloux, Belgium). The database was registered with clinicaltrials.gov (NCT00727623). This registry was centrally approved by ethical committee of the Ghent University Hospital (2011/455). Informed consent was obtained from all patients or their legal representatives.

Air pollution recording and data analysis

The pollutant concentration data used in this study were based on the air quality measurements realized by the three Belgian regions and compiled in a database from the Belgian Interregional Environment Agency (CELINE-IRCEL, <http://www.irceline.be>). Sixty-five automatic stations located across Belgium in both urbanized and rural areas assessed PM₁₀ concentrations, 38 assessed PM_{2.5}, 41 measured O₃ and 93 assessed NO₂. Based on these air pollutants measurements and an interpolation method, and after adjustment for population density, a national daily 24-hour average was obtained for each pollutant. This index reflects the background level of air pollution exposure which Belgian population is exposed to. In brief, a statistical air pollution interpolation method, called RIO, was developed and validated and has been applied in Belgium since 2007 to provide a real-time

assessment of the ambient air quality[19]. The first step of the process is to remove the local nature of air pollution measurements based on a land use indicator. Site-independent data are then interpolated via a standard interpolation technique ("ordinary kriging"). Finally, the local bias is added back again to the interpolation results. After the interpolation, the spatial average is weighted in function of the population density in each grid cell of the RIO map (Figure 1).

Daily mean atmospheric temperature (in degrees Celsius) was obtained from the Royal Meteorological Institute of Belgium (RMIB).

Study design

As previously reported in studies of ambient air pollution and myocardial infarction[11,14], we used a time-stratified case-crossover design. This design is comparable to a matched case-control study. However, instead of comparing exposure between people experiencing a STEMI (case) and people who did not (control), pollutant concentrations before the STEMI (case period) were compared with other randomly selected periods, when the subject did not experience a STEMI (control periods). Because case periods and their matched control periods are derived from the same person, time-independent confounders, such as age, comorbidities, and smoking status are controlled by the case-crossover study design. However, variables that change between case and control time periods are possible confounders. These potential confounders explain why weather conditions, which vary over short time periods, were included in our statistical models. In time-stratified case-crossover, the stratification can be indeed tailored to match the most important time-dependent confounders. Stratifying by year and month is adequate for most studies and can be done as well by day of the week and temperature[14][20].

Statistical analysis

Because most of the effect of pollution on the acute myocardial infarction risk is seen within one day of exposure[11][21], our main analysis focused directly on 0-day lag time between exposure and STEMI. Odds ratios (OR) and 95% confidence intervals (CI) were calculated with a conditional logistic regression model using R software 3.0.2 (The R Foundation for Statistical Computing) with the season package[22]. Risk estimates were performed for a $10 \mu\text{g}/\text{m}^3$ increase in air pollutants and a 10°C increase in temperature. The population attributable fraction (PAF) was calculated using $(\text{OR}-1)/\text{OR}$, taking into account 100% exposure to environmental triggers. The relation among pollutants and temperature was assessed using Spearman's correlation coefficient. Significance was assumed when p was <0.05 .

We performed a sensitivity analysis to consider also the day-of-week effects by matching rather than explicit adjustment for a covariable added into the model. In all models, case periods were defined as the day of hospitalization for STEMI. In model 1, case and control days were matched by a mean temperature of $\pm 2^\circ\text{C}$. The controls were selected in a one-month stratum with a 4-day exclusion period around the event day to ensure a control by design of the seasonal effect. The day of the week was also added as confounder in the model. In model 2, case and control days were matched by the day of the week and adjusted for temperature by a simple variable addition in the model. In model 3, temperature and day of the week were injected as co-variables into the model. In model 4, we performed a double matching of control days for both temperature and day of the week.

RESULTS

Population and STEMI characteristics

The population characteristics are summarized in Table 1. During our 5 years study period, 11,428 patients were hospitalized for STEMI. The patients were 62.8 ± 13.4 years old and were predominantly male (75.4%). Hypertension was present in 42.9%, 16.9% had a history of coronary artery disease, and 14.7% had diabetes.

STEMI incidence decreased by approximately 1.5% per year during the study period. The daily incidence of STEMI displays discrete seasonal variations (Figure 1), with more events during winter. In a typical example (Figure 2), there were excesses of both air pollution and STEMI on January 17th 2012, compared with two weeks earlier.

Most STEMI patients were low-risk STEMI patients (TIMI score $\text{TIMI} \leq 3$ in 47.5% of patients) and had no evidence of heart failure (90.1% of patients with Killip class ≤ 2). The incidence of cardiac arrest as the initial presentation of STEMI was 10.5%. Primary PCI was performed in 89.6% of patients, 2.8% of patients were treated by means of thrombolysis, and the remainder being treated conservatively. The overall in-hospital STEMI mortality rate was 6.8%.

Air pollution characteristics

The distributions of ambient particle concentrations, NO_2 and O_3 and temperature during the study period are presented in Table 2. The median $\text{PM}_{2.5}$ concentration was $12.4 \mu\text{g}/\text{m}^3$, with 5th and 95th percentiles of 5.1 and $39.8 \mu\text{g}/\text{m}^3$, respectively. The annual mean concentration of $\text{PM}_{2.5}$ was $16.1 \pm 11.4 \mu\text{g}/\text{m}^3$. Daily concentrations of the different pollutants display detectable seasonal variation, with elevated concentrations during the winter for PM_{10} , $\text{PM}_{2.5}$ and NO_2 and a higher O_3 concentration during the summer (Figure 1). PM_{10} ,

PM_{2.5} and NO₂ were negatively correlated with ambient air temperature, whereas O₃ was positively correlated with ambient air temperature (Table 3).

Global effect of AP on STEMI

The adjusted risks of STEMI for each 10 µg/m³ increase in air pollutant are presented in Figure 3. Each 10 µg/m³ increase in PM₁₀, PM_{2.5} and NO₂ was associated with an increased odds ratio (OR) of STEMI of 1.026 (CI_{95%}: 1.005-1.048), 1.028 (CI_{95%}: 1.003-1.054) and 1.051 (CI_{95%}: 1.018-1.084), respectively. No effect of O₃ was found. The PAF for PM₁₀, PM_{2.5} and NO₂ were 2.53, 2.72 and 4.85%, respectively.

Subgroup analysis of the effect of AP on STEMI

The risks of STEMI associated with each 10 µg/m³ increase in air pollutant, stratified by patient characteristics, are shown in Table 4. These associations between air pollutants and STEMI were only significant among men (all p<0.05). STEMI was associated with PM₁₀ exposure in patients ≥75 years of age (OR: 1.046, CI_{95%}: 1.002-1.092) and NO₂ in patients ≤54 years old (OR: 1.071, CI_{95%}: 1.010-1.136). No differences in air pollutant relative risk estimates regarding diabetes, AHT or previous CAD were found. A subgroup analysis according to Belgium regions observed a similar trend into the air pollutant effects than those observed in the entire population.

Air pollution was not associated with a higher incidence of cardiac arrest at presentation in this STEMI population. In addition, we did not observe an association between air pollution and in-hospital mortality.

Sensitivity analysis

In all the models, effect of O₃ was not significant (data not shown). For PM₁₀ and PM_{2.5}, the first three methods produce very similar results (Table S1). In contrast, for NO₂, the strongest associations were observed with the time-stratified and temperature matched case-crossover method used for our final analysis. No significant effect of air pollution on the risk to develop a STEMI was observed when a double matching of control days for both day of the week and temperature was performed (model 4).

DISCUSSION

Based on data from the Belgian STEMI registry and air pollution monitoring provided by the Belgian Environmental Agency, we demonstrated that increased ambient PM_{2.5} and NO₂ concentrations were associated with an increased risk of hospitalization for STEMI. For PM_{2.5}, each 10 $\mu\text{g.m}^{-3}$ increase was associated with a 2.8% increase in STEMI hospitalization. The effect of NO₂ exceeded that of PM_{2.5}, with a 5.1% increase in STEMI hospitalization for every 10 $\mu\text{g.m}^{-3}$ increase in this pollutant. Finally, other baseline comorbidities or baseline characteristics did not affect the relationship between STEMI and pollution exposure, nor did we find a relationship with in-hospital mortality.

To our knowledge, our study is the first that has considered the effect of AP on the STEMI occurrence at a comprehensive, nationwide level. Our observations were based on an original method, which addresses how an index of background air pollution exposure, which Belgian population is exposed to, affects the onset of STEMI. Above methodological novelties, our main new finding relies on the effect of NO₂, a gaseous air pollutant more specifically related to diesel exhaust, which far exceeds the impact of fine particles. We believe that this result is particularly important because of the growing problematic of air pollution in Europe[23], and the fact that our observations were made despite “safe” levels of pollutant concentrations according to EU legislation. The annual concentrations observed in our study of PM₁₀, PM_{2.5} and NO₂ remained below the respective 40, 25 and 40 $\mu\text{g}/\text{m}^3$ standard defined by the European legislation[24]. Interestingly, in contrast to European legislation, the WHO recommends 20 and 10 $\mu\text{g}/\text{m}^3$ for the mean annual concentrations of PM₁₀ and PM_{2.5}[25], which are more restrictive and often exceeded in Belgium at the time of our study.

Few studies have investigated the association between air pollution and the type of myocardial infarction. As illustrated (Table S2A and S2B), most of these studies rely on

subgroup analysis from large administrative databases[12,13,26–28], and differ from our study which is based on a dedicated STEMI registry. An earlier mono-centric study performed in a small group of patients (n=338) who lived close to an air pollution monitoring centre (maximum 25 km) showed an 18% STEMI risk increase with a $7.1 \mu\text{g}/\text{m}^3$ increase in PM_{2.5} exposure[13]. Interestingly, the elevated risk was associated with exposure in the hour prior to the acute coronary syndrome, suggesting an acute effect of particulate exposure on vasomotor tone, platelet function or plaque vulnerability. In another study, which was restricted to transmural infarctions, each $10.8 \mu\text{g}/\text{m}^3$ increase in PM_{2.5} was associated with a 10% increase in STEMI[12]. More recently, in another subgroup study of acute myocardial infarction population, a 15% increase in STEMI was observed with a $10 \mu\text{g}/\text{m}^3$ increase in PM_{2.5} exposure[26]. At the opposite, 3 other studies failed to demonstrate an effect of fine particle on the risk of STEMI[27–29]. In our study, the effect of PM₁₀ and PM_{2.5} is lower than those previously reports but may be more in line with results of meta-analysis showing a 2 to 2.5% increase in myocardial infarction for every $10 \mu\text{g}/\text{m}^3$ increase in PM[21]. Our finding that men but not women were significantly affected by air pollution remains largely unexplained but might be partially caused by the underrepresentation of women in our cohort (less than 25%).

Aside from PM effect, the strongest association observed here was between STEMI and NO₂. Despite the absence of a clear association between NO₂ and myocardial infarction in early trials[30], our results are congruent with more recent studies suggesting that higher levels of NO₂ could be associated with a transient increased risk of myocardial infarction[10],[31],[32] and cardiovascular mortality[33]. Our data also suggest that younger patients more often develop STEMI in relation with NO₂ exposure. Because NO₂ is related to traffic vehicle emission[34], we hypothesize that the younger population may be exposed more to NO₂ due to higher levels of social and professional activities. However, our results

regarding NO₂ need to be tempered. The local situation of Belgium[34], characterized by a high penetrance of diesel vehicle representing 61% of personal-use vehicles, in a country where 49% of NO_x emission (including NO₂) are mediated by road transport, may limit the extrapolation of our results to other countries. Furthermore, our sensitivity analysis demonstrates that contrary to PM, effect of NO₂ does not reach statistical significance if the day-of-week effect was addressed by matching rather than adjustment for a covariable. However, we believe that our method, which matches the control days for temperature, instead of adding the temperature as a simple covariable into the model[35], ensures a more reliable control of the temperature confounding effect. Indeed temperature effect on STEMI is complex, and observed not only at low but also at high temperature[16]. A double matching of control days on both temperature and day of the week would be ideal but, as shown in the sensitivity analysis, reduces dramatically the statistical power of the analysis by reducing the number of potential available control days. Finally, we independently analysed the association of each pollutant with the risk of STEMI and the potential interactions among pollutant, as for example NO₂ and PM_{2.5}, were not addressed in our study.

Beside the control of confounding factors, a major issue in studies evaluating the health effect of air pollution emerges from the methods used to assess pollution exposure. As illustrated (Table S2B), most of the studies relies on a different methodological approach for air pollution exposure assessment, and this may account for the previously mentioned results discrepancy observed between studies[36,37]. In most studies, individual exposure is extrapolated from a fixed monitoring stations[38], or are based on a population exposure index calculated a raw mean of pollutant concentrations recorded by a panel of stations presented in the region of interest[26][29][39]. Such approaches make important assumptions especially on spatial and temporal variability of air pollution and may generate a misclassification of individual exposure[40]. Indeed, studies suggest that individual exposure

level cannot be extrapolated from a fixed station[38,41]. For these reasons, we adopt in our study a population-based approach considering an interpolation modelling to provide a national evaluation of air pollution exposure. Thanks to population density adjustment, this methodology accounts for a non-uniform population distribution across the country. Furthermore the risk of a regional exposure misclassification appears marginal because similar trends of PM and NO₂ effects were observed in both North and South part of Belgium. Regarding the absence of a validated methodology to appropriately evaluate pollution exposure, our result offer new insights into the acute cardiovascular effects of air pollution by means of an innovative methodology.

As other potential study limitations, the time of symptom onset was also not available in a sufficient number of patients to allow for an analysis of very short-term associations between air pollution exposure and STEMI. Similarly, as our analysis focuses directly on the effect of 24h pollution exposure before the event, our study does not provide information on possible long-term associations. While being nationwide and compulsory, our registry covers an estimated 60% of all STEMI patients in Belgium but this should not affect the relative risk as assessed in this time-stratified case-crossover design.

In conclusion, particulate and NO₂ air pollution are associated with an increased risk of STEMI independent of classical cardiovascular risk factors and despite air pollution exposure levels for the Belgian population that are in accordance with the European air quality legislation.

REFERENCES

- [1] C.B.B. Guerreiro, V. Foltescu, F. de Leeuw, Air quality status and trends in Europe, *Atmos. Environ.* 98 (2014) 376–384.
- [2] B. Nemery, P.H. Hoet, A. Nemmar, The Meuse Valley fog of 1930: an air pollution disaster., *Lancet.* 357 (2001) 704–8.
- [3] World Health Organization, The world health report 2002 - Reducing Risks, Promoting Healthy Life, 2002.
- [4] B. Brunekreef, Air pollution and life expectancy: is there a relation?, *Occup. Environ. Med.* 54 (1997) 781–4.
- [5] D.E. Newby, P.M. Mannucci, G.S. Tell, A.A. Baccarelli, R.D. Brook, K. Donaldson, F. Forastiere, M. Franchini, O.H. Franco, I. Graham, G. Hoek, B. Hoffmann, M.F. Hoylaerts, N. Künzli, N. Mills, J. Pekkanen, A. Peters, M.F. Piepoli, S. Rajagopalan, R.F. Storey, Expert position paper on air pollution and cardiovascular disease., *Eur Heart J.* 36 (2015) 83-93b .
- [6] G. Cesaroni, F. Forastiere, M. Stafoggia, Z.J. Andersen, C. Badaloni, R. Beelen, B. Caracciolo, U. de Faire, R. Erbel, K.T. Eriksen, L. Fratiglioni, C. Galassi, R. Hampel, M. Heier, F. Hennig, A. Hilding, B. Hoffmann, D. Houthuijs, K.-H. Jöckel, M. Korek, T. Lanki, K. Leander, P.K.E. Magnusson, E. Migliore, C.-G. Ostenson, K. Overvad, N.L. Pedersen, J.P. J, J. Penell, G. Pershagen, A. Pyko, O. Raaschou-Nielsen, A. Ranzi, F. Ricceri, C. Sacerdote, V. Salomaa, W. Swart, A.W. Turunen, P. Vineis, G. Weinmayr, K. Wolf, K. de Hoogh, G. Hoek, B. Brunekreef, A. Peters, Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE Project., *BMJ.* 348 (2014) f7412.
- [7] H. Mustafic, P. Jabre, Main Air Pollutants and Myocardial Infarction, *JAMA.* 307 (2012) 713–721.
- [8] D. Nuvolone, D. Balzi, M. Chini, D. Scala, F. Giovannini, A. Barchielli, Short-Term association between ambient air pollution and risk of hospitalization for acute myocardial infarction: Results of the cardiovascular risk and air pollution in Tuscany (RISCAT) study, *Am. J. Epidemiol.* 174 (2011) 63–71.
- [9] R.D. Brook, B. Franklin, W. Cascio, Y. Hong, G. Howard, M. Lipsett, R. Luepker, M. Mittleman, J. Samet, S.C. Smith, I. Tager, Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association., *Circulation* (2004) 2655–2671.
- [10] K. Bhaskaran, S. Hajat, B. Armstrong, A. Haines, E. Herrett, P. Wilkinson, L. Smeeth, The effects of hourly differences in air pollution on the risk of myocardial infarction: case crossover analysis of the MINAP database, *BMJ.* 343 (2011) d5531–d5531.
- [11] P. Collart, Y. Coppieters, G. Mercier, V. Massamba Kubuta, A. Leveque, Comparison of four case-crossover study designs to analyze the association between air pollution exposure and acute myocardial infarction., *Int. J. Environ. Health Res.* (2015) 1–13.
- [12] D.Q. Rich, H.M. Kipen, J. Zhang, L. Kamat, A.C. Wilson, J.B. Kostis, Triggering of transmural infarctions, but not nontransmural infarctions, by ambient fine particles., *Environ. Health Perspect.* 118 (2010) 1229–1234.
- [13] B. Gardner, F. Ling, P.K. Hopke, M.W. Frampton, M.J. Utell, W. Zareba, S.J.

- Cameron, D. Chalupa, C. Kane, S. Kulandhaisamy, M.C. Topf, D.Q. Rich, Ambient fine particulate air pollution triggers ST-elevation myocardial infarction, but not non-ST elevation myocardial infarction: a case-crossover study., *Part. Fibre Toxicol.* 11 (2014).
- [14] H. Janes, L. Sheppard, T. Lumley, Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias., *Epidemiology.* 16 (2005) 717–26.
- [15] K. Wolf, A. Schneider, S. Breitner, S. von Klot, C. Meisinger, J. Cyrys, H. Hymer, H.-E. Wichmann, A. Peters, Air temperature and the occurrence of myocardial infarction in Augsburg, Germany., *Circulation.* 120 (2009) 735–42.
- [16] S. Lee, E. Lee, M.S. Park, B.Y. Kwon, H. Kim, D.H. Jung, K.H. Jo, M.H. Jeong, S.-W. Rha, Short-term effect of temperature on daily emergency visits for acute myocardial infarction with threshold temperatures., *PLoS One.* 9 (2014) e94070.
- [17] S.A. Gevaert, D. De Bacquer, P. Evrard, C. Convens, P. Dubois, J. Boland, M. Renard, C. Beauloye, P. Coussement, H. De Raedt, A. de Meester, E. Vandecasteele, P. Vranckx, P.R. Sinnaeve, M.J. Claeys, Gender, TIMI risk score and in-hospital mortality in STEMI patients undergoing primary PCI: results from the Belgian STEMI registry., *EuroIntervention.* 9 (2014) 1095–101.
- [18] E.H. Vandecasteele, M. De Buyzere, S. Gevaert, A. de Meester, C. Convens, P. Dubois, J. Boland, P. Sinnaeve, H. De Raedt, P. Vranckx, P. Coussement, P. Evrard, C. Beauloye, M. Renard, M.J. Claeys, Reperfusion therapy and mortality in octogenarian STEMI patients: results from the Belgian STEMI registry., *Clin. Res. Cardiol.* 102 (2013) 837–45.
- [19] S. Janssen, G. Dumont, F. Fierens, C. Mensink, Spatial interpolation of air pollution measurements using CORINE land cover data, *Atmos. Environ.* 42 (2008) 4884–4903.
- [20] H. Scheers, S.M. Mwalili, C. Faes, F. Fierens, B. Nemery, T.S. Nawrot, Does air pollution trigger infant mortality in Western Europe? A case-crossover study., *Environ. Health Perspect.* 119 (2011) 1017–22.
- [21] T.S. Nawrot, L. Perez, N. Künzli, E. Munters, B. Nemery, Public health importance of triggers of myocardial infarction: a comparative risk assessment., *Lancet.* 377 (2011) 732–740.
- [22] A.G. Barnett, P. Baker, A.J. Dobson, Analysing seasonal data, *R J.* 4 (2012) 5–10.
- [23] Status and trends of NO₂ ambient concentrations in Europe.
http://acm.eionet.europa.eu/reports/ETCACC_TP_2010_19_NO2trends (accessed 19.03.15).
- [24] Directive 2008/50/EC of the European Parliament and of the Council of 21 May 2008 on ambient air quality and cleaner air for Europe, (2008). <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32008L0050> (accessed 19.03.15).
- [25] World Health Organization WHO Air quality guidelines - global update (2005); http://www.euro.who.int/__data/assets/pdf_file/0005/78638/E90038.pdf (accessed 19.03.15)
- [26] C.A. Pope, J.B. Muhlestein, J.L. Anderson, J.B. Cannon, N.M. Hales, K.G. Meredith, V. Le, B.D. Horne, Short-Term Exposure to Fine Particulate Matter Air Pollution Is Preferentially Associated With the Risk of ST-Segment Elevation Acute Coronary Events, *J. Am. Heart Assoc.* 4 (2015) e002506.

- [27] X. Wang, W. Kindzierski, P. Kaul, Comparison of transient associations of air pollution and AMI hospitalisation in two cities of Alberta, Canada, using a case-crossover design, *BMJ Open*. 5 (2015) e009169–e009169.
- [28] A. Milojevic, P. Wilkinson, B. Armstrong, K. Bhaskaran, L. Smeeth, S. Hajat, Short-term effects of air pollution on a range of cardiovascular events in England and Wales: case-crossover analysis of the MINAP database, hospital admissions and mortality., *Heart*. 100 (2014) 1093–8.
- [29] C. Caussin, S. Escolano, H. Mustafic, S. Bataille, M. Tafflet, E. Chatignoux, Y. Lambert, H. Benamer, P. Garot, P. Jabre, L. Delorme, O. Varenne, E. Teiger, B. Livarek, J.-P. Empana, C. Spaulding, X. Jouven, Short-term exposure to environmental parameters and onset of ST elevation myocardial infarction. The CARDIO-ARSIF registry., *Int. J. Cardiol*. 183C (2015) 17–23.
- [30] J.-B. Ruidavets, M. Cournot, S. Cassadou, M. Giroux, M. Meybeck, J. Ferrières, Ozone air pollution is associated with acute myocardial infarction., *Circulation*. 111 (2005) 563–9.
- [31] J.E. Hart, E.B. Rimm, K.M. Rexrode, F. Laden, Changes in traffic exposure and the risk of incident myocardial infarction and all-cause mortality., *Epidemiology*. 24 (2013) 734–42.
- [32] W.B. Goggins, E.Y.Y. Chan, C.-Y. Yang, Weather, pollution, and acute myocardial infarction in Hong Kong and Taiwan., *Int. J. Cardiol*. 168 (2013) 243–9.
- [33] L. Stockfelt, E.M. Andersson, P. Molnár, A. Rosengren, L. Wilhelmsen, G. Sallsten, L. Barregard, Long term effects of residential NO_x exposure on total and cause-specific mortality and incidence of myocardial infarction in a Swedish cohort., *Environ. Res*. 142 (2015) 197–206.
- [34] European Environment Agency (EEA). Belgium air pollution country fact sheet. 2014. <http://www.eea.europa.eu/themes/air/air-pollution-country-fact-sheets-2014> (accessed 26/01/2016).
- [35] M.J. Claeys, S. Coenen, C. Colpaert, J. Bilcke, P. Beutels, K. Wouters, V. Legrand, P. Van Damme, C. Vrints, Environmental triggers of acute myocardial infarction: results of a nationwide multiple-factorial population study., *Acta Cardiol*. 70 (2015) 693–701.
- [36] Y. Sellier, J. Galineau, A. Hulin, F. Caini, N. Marquis, V. Navel, S. Bottagisi, L. Giorgis-Allemand, C. Jacquier, R. Slama, J. Lepeule, Health effects of ambient air pollution: do different methods for estimating exposure lead to different results?, *Environ. Int*. 66 (2014) 165–73.
- [37] M.L. Bell, The use of ambient air quality modeling to estimate individual and population exposure for human health research: a case study of ozone in the Northern Georgia Region of the United States., *Environ. Int*. 32 (2006) 586–93.
- [38] S. Steinle, S. Reis, C.E. Sabel, Quantifying human exposure to air pollution--moving from static monitoring to spatio-temporally resolved personal exposure assessment., *Sci. Total Environ*. 443 (2013) 184–93.
- [39] Q. Zhang, W. Qi, W. Yao, M. Wang, Y. Chen, Y. Zhou, Ambient Particulate Matter (PM_{2.5}/PM₁₀) Exposure and Emergency Department Visits for Acute Myocardial Infarction in Chaoyang District, Beijing, China During 2014: A Case-Crossover Study., *J. Epidemiol*. (2016).
- [40] L.K. Baxter, K.L. Dionisio, J. Burke, S. Ebelt Sarnat, J.A. Sarnat, N. Hodas, D.Q.

- Rich, B.J. Turpin, R.R. Jones, E. Mannshardt, N. Kumar, S.D. Beevers, H. Özkaynak, Exposure prediction approaches used in air pollution epidemiology studies: key findings and future recommendations., *J. Expo. Sci. Environ. Epidemiol.* 23 654–9.
- [41] F.S. Violante, A. Barbieri, S. Curti, G. Sanguinetti, F. Graziosi, S. Mattioli, Urban atmospheric pollution: personal exposure versus fixed monitoring station measurements., *Chemosphere.* 64 (2006) 1722–9.

TABLES

Table 1. Characteristics of the study population		
	n	%
Study periods		
2009	2668	23.4
2010	2475	21.7
2011	2264	19.8
2012	2065	18.1
2013	1948	17.1
Patients characteristics		
Age		
≥ 75	2598	22.7
55-74	5467	47.9
≤ 54	3355	29.4
Male		
AHT	8607	75.4
Diabetes mellitus	4906	42.9
Known CAD	1678	14.7
Known PAD	1934	16.9
Known PAD	963	8.4
Clinical presentation		
TIMI risk score		
0-3	5434	47.5
4-8	5010	43.8
9-14	984	8.6
Killip Class		
1-2	10297	90.1
3-4	1131	9.9
Treatment modalities		
Primary PCI	10239	89.6
Rescue PCI	172	1.5
Facilitated PCI	137	1.2
Thrombolysis	320	2.8
No reperfusion	560	4.9

Abbreviations: AHT: arterial hypertension, CAD: coronary artery disease, PAD: peripheral artery disease, TIMI score: Thrombolysis In Myocardial Infarction risk score, PCI: percutaneous coronary intervention.

Table 2. Temperature and air pollution levels in Belgium, 2009 – 2013.

	Percentiles					Mean $\pm$ sd
	5%	25%	50%	75%	95%	
Temperature (°C)	-1.1	6.0	11.0	15.7	20.8	10.6 $\pm$ 6.7
PM₁₀ (µg/m ³)	10.0	14.9	20.2	29.3	50.2	23.9 $\pm$ 13.2
PM_{2.5} (µg/m ³)	5.1	8.2	12.4	20.4	39.8	16.1 $\pm$ 11.4
NO₂ (µg/m ³)	10.3	15.9	22.0	30.1	42.4	23.7 $\pm$ 10.2
O₃ (µg/m ³)	10.9	28.8	42.0	54.2	71.3	10.6 $\pm$ 6.7

Abbreviations: PM₁₀: particulate matter with aerodynamic diameter <10 µm; PM_{2.5}: particulate matter with aerodynamic diameter <2.5 µm; NO₂: nitrogen dioxide; O₃: ozone.

Table 3. Matrix of Spearman correlation coefficients between air pollutants and temperature.

	Temperature	PM ₁₀	PM _{2.5}	NO ₂
PM ₁₀	-0.204	-	-	-
PM _{2.5}	-0.326	0.951	-	-
NO ₂	-0.482	0.738	0.771	-
O ₃	0.513	-0.287	-0.388	-0.600

Abbreviations: PM₁₀: particulate matter with aerodynamic diameter <10 µm; PM_{2.5}: particulate matter with aerodynamic diameter <2.5 µm; NO₂: nitrogen dioxide; O₃: ozone.

Table 4: Patient subgroup analysis

	OR	PM 10 CI 95%	P	OR	PM 2.5 CI 95%	p	OR	NO ₂ Ci 95%	p
Age									
≥ 75 (n=2598)	1.046	[1.002;1.092]	0.041	1.049	[0.996;1.105]	0.068	1.063	[0.996;1.135]	0.065
55 – 74 y.o (n=5467)	1.015	[0.985;1.047]	0.321	1.015	[0.979;1.052]	0.425	1.032	[0.986;1.080]	0.173
≤ 54 y.o (n=3355)	1.028	[0.989;1.068]	0.156	1.034	[0.988;1.082]	0.153	1.071	[1.010;1.136]	0.021
Sex									
Male (n= 8 607)	1.031	[1.007;1.056]	0.011	1.034	[1.027;1.105]	0.020	1.065	[1.027;1.105]	<0.001
Female (n= 2 813)	1.011	[0.968;1.055]	0.631	1.009	[0.959;1.063]	0.720	1.006	[0.944;1.073]	0.847
Risk factor									
AHT (n=4 906)	1.020	[0.989;1.053]	0.213	1.021	[0.983;1.061]	0.280	1.030	[0.982;1.080]	0.229
Diabete (n= 1 678)	1.008	[0.956;1.063]	0.770	1.005	[0.942;1.072]	0.879	1.019	[0.939;1.107]	0.641
Known CAD (n=1 934)	1.015	[0.965;1.067]	0.569	1.020	[0.960;1.083]	0.527	1.041	[0.966;1.124]	0.288
Known PAD (n=963)	1.023	[0.953;1.099]	0.525	1.032	[0.947;1.124]	0.472	1.031	[0.928;1.147]	0.567
Region*									
South (n=3036)	1.027	[0.987;1.069]	0.190	1.026	[1.001; 1.052]	0.043	1.070	[1.007;1.137]	0.030
North (n = 8343)	1.026	[1.004;1.048]	0.020	1.029	[1.000.1.059]	0.049	1.045	[1.009.1.082]	0.014
Cardiac arrest (n=1205)	0.971	[0.911 ;1.035]	0.366	0.977	[0.906 ;1.053]	0.541	0.980	[0.889; 1.079]	0.677
In hospital mortality (n=774)	1.039	[0.960 ;1.126]	0.342	1.062	[0.966 ;1.168]	0.214	1.006	[0.893 ;1.132]	0.926

OR expressed for a 10 µg.m-3 increase in air pollutant. *North part of Belgium includes Brussels. Abbreviations: PM₁₀: particulate matter with aerodynamic diameter <10 µm, PM_{2.5}: particulate matter with aerodynamic diameter <2.5 µm, NO₂: nitrogen dioxide, AHT: arterial hypertension, CAD: coronary artery disease, PAD: peripheral artery disease.

FIGURE LEGENDS

Figure 1: Seasonal variation of the number of STEMI, PM_{2.5}, NO₂ and O₃ concentrations.

Figure 2: Illustrative example of air pollution exposure and STEMI cases observed in Belgium on 2 different days in January 2012

The RIO maps of the PM₁₀ on 05/01/2012 and 17/01/2012 are presented. The RIO interpolation mode was developed to incorporate both regional and local aspects of the air pollution phenomenon and produced a concentration estimates on a 4x4 km² grid, which is adjusted for the population density living within the grid cell. Both non adjusted (supra) and adjusted (infra) maps for population density are presented.

Figure 3: Effect of air pollution on the risk of STEMI

Odds ratio of STEMI are expressed for a 10 µg.m⁻³ increase in air pollutant concentration. The odds ratios are adjusted for ambient air temperature, day of the week and season. Abbreviations: STEMI: ST elevation myocardial infarction, PM: particle matter, NO₂: nitrogen dioxide.

Figure 1:

Figure 2

Figure 3: