Environment International 119 (2018) 334–345

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Perturbation of metabolic pathways mediates the association of air pollutants with asthma and cardiovascular diseases

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ARTICLE INFO

Handling Editor: Yong Guan Zhu

Keywords:
Air pollution
Untargeted metabolomics
Metabolic pathways
Adult-onset asthma
Cardio-cerebrovascular diseases

ABSTRACT

Background: Epidemiologic evidence indicates common risk factors, including air pollution exposure, for respiratory and cardiovascular diseases, suggesting the involvement of common altered molecular pathways.
Objectives: The goal was to find intermediate metabolites or metabolic pathways that could be associated with both air pollutants and health outcomes ("meeting-in-the-middle"), thus shedding light on mechanisms and reinforcing causality.
Methods: We applied a statistical approach named 'meet-in-the-middle' to untargeted metabolomics in two independent case-control studies nested in cohorts on adult-onset asthma (AOA) and cardio-cerebrovascular diseases (CCVD). We compared the results to identify both common and disease-specific altered metabolic pathways.
Results: A novel finding was a strong association of AOA with ultrafine particles (UFP; odds ratio 1.80 [1.26, 2.55] per increase by 5000 particles/cm^3). Further, we have identified several metabolic pathways that potentially mediate the effect of air pollution on health outcomes. Among those, perturbation of Linoleate metabolism pathway was associated with air pollution exposure, AOA and CCVD.

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https://doi.org/10.1016/j.envint.2018.06.025
Received 8 March 2018; Received in revised form 24 May 2018; Accepted 20 June 2018

Conclusions: Our results suggest common pathway perturbations may occur as a consequence of chronic exposure to air pollution leading to increased risk for both AOA and CCVD.

1. Introduction

Asthmatics often suffer from comorbidities including cardiovascular diseases. Comorbidity influences the disease prognosis and control. Refractory asthma is more likely to manifest with cardiovascular comorbidity than controlled asthma (Hekking et al., 2018). Asthma and cardiovascular disease share common risk factors such as smoking, obesity, aging and air pollution exposure, consistent with common molecular pathways altered in the etiology of diseases.

Short-term effects of air pollution exposure on asthma exacerbation have long been established in adults and in children (Peel et al., 2005; Schwartz et al., 1993; Sunyer et al., 1997). The role of air pollution in asthma onset is less conclusive, particularly in adults (Anderson et al., 2013; Jacquemin et al., 2012). Only a few studies used individually assigned exposure estimates to study the effects of ambient air pollution on adult-onset asthma. The largest study sample was based on over 600,000 subjects, including 27,000 asthmatics, and demonstrated an association of PM_{10} exposure – derived from a pan-European land use regression model – with asthma prevalence (Cai et al., 2017). The 'European Study of Cohorts for Air Pollution Effects' (ESCAPE) reported a positive but not statistically significant association with asthma incidence in adults for all air pollution metrics (NO_2, NO, PM_{10}, $PM_{2.5}$, traffic load; traffic intensity) except PM_{coarse} (Jacquemin et al., 2015). In the Swiss SAPALDIA cohort, long term improvement in air pollution levels was associated with an attenuated age-related lung function decline (Downs et al., 2007), with a decreased prevalence of respiratory symptoms including wheezing and breathlessness (Schindler et al., 2009), and with a decreased onset of asthma in adults (Kunzli et al., 2009).

In addition, a growing number of epidemiological studies showed that air pollution is associated with coronary artery disease (McGuinn et al., 2016; Wolf et al., 2015), cardiovascular diseases (Brook et al., 2010; Franklin et al., 2015), and cerebrovascular diseases (Stafoggia et al., 2014) including ischemic stroke (Chung et al., 2017; Cox Jr, 2017). A recent meta-analysis within ESCAPE showed that increases in $PM_{2.5}$ and PM_{10} were associated with risks of fatal and total coronary events, respectively (Cesaroni et al., 2014), and increased risk for cerebrovascular diseases was reported for higher exposure to $PM_{2.5}$ and NO_2(Stafoggia et al., 2014).

Ultrafine particles (UFP) exposure has been less studied than exposure to larger particles, and no regulatory agencies have established guidelines for UFP so far. Compared to larger particulate matter, UFP have distinctive characteristics that may lead to higher toxicity: their extremely small size allows them to reach deeper into the tissues and evade clearance, and higher surface-to-mass ratio facilitates adhesion of larger amounts of hazardous materials. Whether this indeed translates into a higher risk of respiratory or cardiovascular diseases in humans remains to be ascertained (Herbert and Kumar, 2017).

The biological mechanisms explaining the effects of air pollution on asthma and its phenotypes and cardio- and cerebrovascular disease (CCVD) are still poorly understood. The best studied putative biological mechanism is oxidative stress caused by air pollutants, followed by pulmonary and systemic inflammation (Guarnieri and Balmes, 2014; Herbert and Kumar, 2017; Newby et al., 2015; Uzoigwe et al., 2013). Previous studies investigating the association between long-term exposure to air pollution and various inflammatory blood biomarkers reported inconsistent results, concerning specific cytokines and pro- or anti-inflammatory effects (Chuang et al., 2011; Fiorito et al., 2018; Mostafavi et al., 2015).

Large-scale profiling of small molecules in biological samples has become available recently, opening the door to the agnostic interrogation of disease processes at the molecular level in epidemiological settings. The metabolome reflects endogenous processes as well as the influences from environment and behaviors, and therefore metabolomics provides a unique opportunity to link genome, exposome, and disease. Metabolomics has been increasingly applied to investigate asthma and major adverse cardiovascular events (Kelly et al., 2017; Kordalewska and Markuszewski, 2015; Shah et al., 2012; Wurtz et al., 2015). However, few studies conducted an untargeted search for blood biomarkers of air pollution exposure (Vlaanderen et al., 2017) or asthma in adults, and none investigated the link between CCVD, asthma and air pollution.

This study was conducted in the framework of EXPOsOMICS, an EU-funded project to investigate the air- and water-borne exposome (Vineis et al., 2017). One of the research questions EXPOsOMICS addresses is the applicability of the 'meet-in-the-middle (MITM)' concept, i.e. intermediate biomarkers as evidence of causality (Vineis et al., 2013). We have applied the MITM approach within two independent case-control studies nested in cohorts: one on adult-onset asthma (AOA) within the SAPALDIA cohort, the other on CCVD within EPIC Italy cohort, and we compared the results to identify both common and disease-specific altered metabolic pathways.

2. Methods

2.1. Study population

2.1.1. Asthma in SAPALDIA

Adult-onset asthma (AOA) metabolomics was studied in a nested case-control study from the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA). A total of 9651 adults were recruited in eight cities representing different geographical and meteorological environments in Switzerland in 1991 (SAPALDIA1); 8047 and 6088 of them participated in the first follow-up in 2001–3 (SAPALDIA2) and in the second follow-up in 2010–11 (SAPALDIA3), respectively. The study protocol was described in detail previously (Ackermann-Liebrich et al., 2005; Martin et al., 1997). The present study examined blood samples from SAPALDIA3. A detailed description of the population cohort and of the study protocol was described in detail previously (Ackermann-Liebrich et al., 2005; Martin et al., 1997). Briefly, asthma cases were selected among the self-reported diagnosis of asthma occurred later than 16 years of age (n = 141) (Siroux et al., 2014) and with archived blood sample available. Controls were randomly sampled among the participants who never reported the following since SAPALDIA1: self-reported asthma; physician-diagnosed asthma; asthma attack in the last 12 months; current asthma medication; wheezing without cold in the last 12 months; three or more asthma-related symptoms in the last 12 months (symptoms considered: breathless while wheezing; woken up with a feeling of chest tightness; attack of shortness of breath after exercise; attack of shortness of breath while at rest; woken by attack of shortness of breath) (Jacquemin et al., 2015) All cases and controls had not smoked for at least 10 years before blood was drawn. Study participants were non-fasted at the time of blood collection and bench time was < 2 h for all but ten cases and five controls. Subjects' characteristics are summarized in Table 1.

2.1.2. Cardio-cerebrovascular diseases in EPIC Italy

Study participants were part of the Italian component (Turin and Varese centers) of the EPICOR study (Bendinelli et al., 2011), which is the cardiovascular section of the European Prospective Investigation