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HEALTH EFFECTS OF LONG-TERM EXPOSURE TO AIR POLLUTION: AN OVERVIEW OF MAJOR RESPIRATORY AND CARDIOVASCULAR DISEASES AND DIABETES•

A large number of studies has provided convincing evidence of adverse effects of exposure to outdoor air pollution on human health, and have served as a basis for current USA and EU Air Quality Standards and limit values. Still, new knowledge is emerging, expanding our understanding of vast effects of exposure to air pollution on human health of this ubiquitous exposure affecting millions of people in urban settings. This paper focuses on the studies of health effects of long-term (chronic) exposures to air pollution, and includes major chronic and acute diseases in adults and especially the elderly, which will present an increasing public health burden, due to improving longevity and projected increasing numbers of elderly. This paper gives an overview of the most relevant and latest literature presented by different health outcomes: chronic obstructive pulmonary disease, asthma, pneumonia, cardiovascular disease, and diabetes.

Keywords: particulate matter; air pollution; long-term exposure; respiratory diseases; cardiovascular diseases; diabetes.

Mounting evidence suggests that air pollution contributes significantly to the global burden of respiratory and cardiovascular diseases, lung cancer, and possibly other cancer types, metabolic diseases, obesity, and diabetes [1-5]. The World Health Organization estimates that particulate matter (PM) air pollution contributes to approximately 800,000 premature deaths each year, ranking it the 13th leading cause of mortality worldwide [1]. Although associations between air pollution and health are complex, a vast number of high quality epidemiologic and experimental studies of varying design, outcome and exposure definition, have lead to an increased recognition and awareness of the emerging importance of traffic-related air pollution, and resulted in a political action and control policies. Numbers of excellent reviews have been written on the health effects of air pollution, but they focus either on a specific disease group, typically on cardiovascular disease [2] or respiratory disease [3], or on a specific component of air pollution, such as reviews specific on PM evidence [1]. An excellent comprehensive review on health effects across different disease and pollution sources of air pollution is over 10 years dated [4]. Similarly, the most recent review focusing specifically on cohort studies and long-term effects of air pollution, which we also cover here, is also dated, providing review of the evidence from Europe only, in 2007 [5]. Thus, in this work, a brief and up-to-date review of literature on the long-term effects of air pollution on major chronic and infectious disease is provided, to reflect a very productive period and a number of high quality studies in last few years. This is not a systematic review, but a short overview over what is perceived by an author as most relevant, and most to date topics and papers on long-term effects of air pollution. This work resulted as a summary of the keynote presentation from the Scientific Meeting Particulate Matter: Research and Mana-

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gement, 3rd WeBIOPATR Workshop & Conference, Belgrade, Serbia, 15-17 November 2011. This paper is organized by the health outcomes, from respiratory and cardiovascular, for which a large evidence base exists, to the 'new' outcomes studied with respect to air pollution, such as diabetes.

RESPIRATORY DISEASE

The plausible biological mechanism of air pollution damage to the lungs involves a local inflammatory response in the lung tissues with a secondary systemic inflammatory response [6]. Repetition of this inhalation injury is believed to be central to the effects of long-term exposure to air pollution and to the chronic and progressive nature of COPD and asthma. With respect to infectious respiratory disease, it is believed that long-term exposure to air pollution and accumulated damage from this exposure in lung tissue predisposes individuals to pneumonia. Specifically, combined with other risk factors, such as age, nutrition, smoking habits, alcohol intake, occupational exposure etc., exposure to air pollution reduces the ability of organism to defend against viruses and bacteria, especially in elderly, thus increasing the risk of pneumonia [7].

Obstructive pulmonary disease (COPD)

COPD is a progressive inflammatory condition of the airways, pulmonary vessels, and lung parenchyma, which is projected to be the third leading cause of death and the fifth leading cause of disability by 2020 [8-10]. Cigarette smoking is responsible for the vast majority of COPD, but it does not explain the increasing prevalence worldwide, and occupational and environmental factors are increasingly thought to play important roles [8-10]. Compelling epidemiological evidence has established that exposure over several days to elevated levels of air pollution exacerbates pre-existing COPD, resulting in increased morbidity and mortality [11]. Solid evidence is, however, lacking for the role of low-level exposure to air pollution in urban environments over years or decades in the development and progression of COPD, due in part to the limited number of prospective cohort studies addressing this problem [8-10]. Most current evidence comes from the studies linking COPD to long-term exposure to indoor air pollution from solid fuel (wood smoke) used for cooking and heating in developing countries [12]. As far as traffic-related air pollution is concerned, long-term exposure was associated with overall and cardiopulmonary mortality [13] and COPD mortality [14], as confirmed in a recent study with multi-pollutant models and improved control for occupational exposures [15]. Several studies have reported link between air pollution and the prevalence of COPD [16-18], and only a single study provided evidence of a link with COPD incidence, defined as first-ever COPD hospitalizations [19]. Impaired lung function, an important measure of respiratory health and a predictor of COPD mortality and morbidity [20], has been associated with long-term exposures to air pollution [17,20,21]. However, two recent studies did not detect a link between lung function and air pollution [22,23].

Asthma

Asthma prevalence is 6-10% in older adults in high-income countries and increasing [24,25], and the economic burden associated with hospital care, medications, and years of work lost due to morbidity and mortality is substantial [26]. Although prevalence of asthma in Eastern Europe and developing world is likely less than 6-10% [27,28], the asthma burden is projected to escalate everywhere, with increasing numbers of older people with asthma due to enhanced longevity [27]. Asthma management among elderly has traditionally focused on diagnosis, and treatment, and less on prevention of exacerbations [29], main determinants of disease severity, and costs [30]. Despite mixed evidence [31], the majority of studies present convincing evidence that air pollution plays an important role in the development and burden of asthma in children [32,33]. There are fewer studies of long-term exposure to air pollution and asthma in elderly than children. Evidence linking chronic exposure to air pollution and adult asthma is based on studies with self-reported asthma prevalence [34] and incidence [35-39], which typically lack information on residential address history, and define exposure to air pollution as a single-year level pollutant mean at recruitment [36] or follow-up [36,37]. In a Swiss cohort study, cumulated levels of modelled traffic-related particulate matter < 10 μm in diameter (PM_{10}) over 11 years were associated with asthma incidence, but only in non smokers [38]. Recently, Danish study has linked exposure to NO_2 for up to 35 years to increased risk of asthma hospitalizations in an elderly cohort [39]. Finally, two studies from Swiss [38] cohort linked improvements in air pollution levels over 11 years to decrease of the lung function decline over the same period [40] and reduced rates of respiratory symptoms [41], providing important clues about the causality between long-term air pollution exposures and chronic respiratory disease, including COPD and asthma.

Pneumonia

Epidemiological evidence regarding the link between air pollution and pneumonia is very limited. Only a single study to date has examined a link between long-term exposure to air pollution and risk of pneumonia [42], a case-control study from Ontario, Canada, which reported a link between long-term exposure to air pollution at home and pneumonia hospitalizations among elderly.

CARDIOVASCULAR DISEASES

Ischemic heart disease (IHD) and ischemic stroke are caused by atherosclerosis disturbing the blood supply to the heart or brain [4]. The biological mechanism of air pollution damage to the blood vessels leading to the heart or brain involves pulmonary inflammation, secondary systemic inflammation, endothelial dysfunction, vasoconstriction, and thrombus formation [1,41,42]. High levels of systemic inflammation biomarkers, high sensitivity C-reactive protein (hs-CRP) and fibrinogen, and independent predictors of cardiovascular disease [43] have been linked to air pollution [44,45], providing a likely link between air pollution and atherosclerosis.

Ischemic heart disease

Epidemiological evidence on the long-term effects on IHD is mixed, yet IHD is still the leading cause of death in many high-income countries [2]. Two Swedish case-control studies failed to find association between air pollution and incident myocardial infarction (MI) while reporting association with fatal events only [48,50]. A study of incident coronary events in Rome found similarly associations with fatal, and only weak associations with non-fatal incident coronary events [49]. Similarly, two studies in women from US Nurses Health studies reported associations only with fatal coronary heart disease events, and none with non-fatal [51,52]. Finally, a single cohort study of women linked air pollution to incidence of IHD and MI [53], whereas cohort of male health professionals failed to find associations with wither fatal of non-fatal incident cardiovascular events [54].

Stroke

Despite detailed knowledge about the impact of years of exposure to tobacco smoke (passive as well as active) on the risk of stroke [2], little has been known about the relevance of related exposure to air pollution for stroke until recently. The current evidence is conflicting [53-60]. A cohort of American women showed an association between air pollution and stroke incidence [53], whereas an American [55] and Norwegian [56] cohorts failed to detect association with stroke mortality. An English ecological study showed excess risk of stroke mortality and stroke hospital admissions in areas with high levels of air pollution [57], but a similar Canadian study failed to link emergency department admissions for stroke to air pollution [58]. None of the studies [53,55-58] distinguished between ischemic and hemorrhagic stroke. A case-control study of ischemic stroke hospitalizations in Sweden failed to detect associations with air pollution [59], whereas a recent cohort study, the first with data on both stroke types, reported significant associations with the ischemic but none with hemorrhagic stroke [60].

DIABETES

The prevalence and incidence of diabetes are rising rapidly, presenting one of the greatest contributors to the global burden of the disease [61]. Environmental exposures linked to industrialization and urbanization, such as air pollution, have not been considered as risk factors for diabetes until recently [62]. In the USA, the prevalence of diabetes correlated with the release of toxicants into the air [63] whereas diabetics appeared more vulnerable than non-diabetics to cardiovascular health effects associated with exposure to air pollution [2]. A plausible biological mechanism of air pollution promoting diabetes was provided by Sun *et al.* [64], showing that exposure to particulate air pollution caused increased blood glucose, inflammation in adipose tissue, and insulin resistance in high-fat-diet mice. Epidemiological evidence is sparse. Prevalence of diabetes was linked to air pollution [65,66], yet only three prospective studies investigated the link between diabetes incidence and air pollution. One study reported significant associations between air pollution and diabetes incidence, but in a small number (n = 87) of women [67], whereas another failed to detect association between air pollution and diabetes incidence, in two large American cohorts [68]. The most recent study found evidence of association between diabetes incidence and air pollution in Danish elderly cohort [69].

OTHER OUTCOMES

Living in areas with increased air pollution levels have been associated with increased overall mortality from natural causes, where cardiopulmonary causes were air pollution contains carcinogenic substances, and is linked to lung cancer [71-76] with convincing amount of evidence. Finally, exposure to air pollution has been convincingly linked to premature morality

and reduced life expectancy [77-83] from all causes, and mainly due to cardiorespiratory causes.

CONLCUSIONS

There is consistent and ample evidence of an effect of long-term exposure to air pollution on premature mortality, cardiovascular mortality, respiratory disease mortality and morbidity, and lung cancer. More data is needed to elucidate whether air pollution causes non-fatal cardiovascular events, diabetes, and pneumonia. High variety in study design, health outcome definition, air pollution exposure assessment, limit the comparability between studies and preclude simple quantitative summaries of the health effects for the purpose of this paper. Future research is needed in several areas: identifying specific sources of air pollution responsible for health effects, especially the role of wood smoke, identifying vulnerable populations, identifying exposures windows through lifetime most relevant for the development of a specific disease, separating short- from long-term effects of air pollution, and studies with better clinically defined health outcomes (for example, subtypes of asthma or stroke may be important to distinguish with respect to relevant effects of air pollution), and better air pollution exposure assessment.

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NAUČNI RAD

ZDRAVSTVENI EFEKTI DUGOTRAJNE IZLOŽENOSTI NA AEROZAGAĐENJE: PREGLED NAJVAŽNIJIH RESPIRATORNIH I KARDIOVASKULARNIH BOLESTI I DIJABETESA

Veliki broj studija obezbedio je ubedljive dokaze o štetnim zdravstvenim efektima usled izloženosti ljudi aerozagađivačima u spoljašnjoj sredini, koji su služe kao osnova za aktuelne standarde o kvalitetu vazduh i granične vrednosti u USA i EU. Još uvek se pojavljuju nova saznanja i proširuju raumevanje o rasprostranjenosti štetnih zdravstvenih efekata izloženosti na aerozagađivače koje tako utiču na milione ljudi u urbanoj sredini. Ovaj rad je usmeren na studije zdravstvenih efekata usled dugotrajne (hronične) izloženosti na aerozagađenje, i uključuje najvažnije hronične i akutne bolesti kod odraslnih i posebno starih, koje predstavljaju dodatno opterećenje na javno zdravlje zbog povećanog broja dugovečnoh i projektovanog povećanja broja starih ljudi. Ovaj rad daje pregled najvažnije i najnovije literaturu koja prikazuje različite zdravstvene ishode: hronične obstruktivne plućne bolesti, pneumoniju, kardiovaskularne bolesti i dijabestes.

Ključne reči: respirabilne četice, aerozagađenje, dugotrajna izloženost, respiratorne bolesti, kardiovaskularne bolesti, dijabetes.