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Air pollution and molecular changes in age-related diseases

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ABSTRACT

Assessment of the impact that air contaminants have on health is difficult as this is a complex mixture of substances that varies depending on the time and place. There are many studies on the association between air pollution and increased morbidity and mortality. Before the effect of polluted air is manifested at the level of the organs, an impact can be observed at the molecular level. These include some new biomarkers, like a shortening of the mean telomere length in DNA, dysregulation of gene expression caused by microRNA levels or a variation in the copy number of mitochondrial DNA. These changes may predispose individuals to premature development of age-related diseases and consequently to shortening of life. The common attribute, shared by changes at the molecular level and the development of diseases, is the presence of oxidative stress.

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Outdoor air pollution; particulate matter; exposure; oxidative stress; aging

Introduction

Outdoor air pollution is a problem that affects a large proportion of the population. Most discussions concern the particulate matter (PM) and a series of gaseous pollutants (such as nitrogen dioxide, sulphur dioxide, ozone). However, this is not just one pollutant, but a complex mixture of substances that may vary depending on the time and place. Furthermore, it also depends on the size of the dust particles, their aerodynamic diameter, the ratio between their length and width, as well as on the structure, surface, age and other parameters of these particles. Bound to those particles to a varying extent are other toxic substances such as heavy metals, organic pollutants, ions, microorganisms and their products, sulphates, nitrates or elemental carbon (Pope and Dockery 2012). Therefore, determining their impact on the health of exposed people is a very delicate matter. Studies usually tend to monitor thoracic fraction, i.e. particle matter with an aerodynamic diameter of 10 micrometres or less (PM_{10}), or respirable fraction, i.e. particle with an aerodynamic diameter of 2.5 micrometres or less ($PM_{2.5}$) (Pope and Dockery 2012). However, experimental studies also focus on particles smaller than 0.1 micrometres, known as ultrafine particles ($PM_{0.1}$) or nanoparticles. The finest nanoparticles are the most hazardous to the human body, as they can distribute from where they entered (via the respiratory system) into the bloodstream and then into other organs and structures (Moreno et al. 2010).

The effects of polluted air at the level of the organs (with a subsequent increase in morbidity and mortality in exposed inhabitants) are preceded by changes at the molecular level. It is considered that those changes include shortening of the mean telomere length, dysregulation of microRNA (miRNA) or a change in the copy number variation (CNV) of

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mitochondrial DNA (mtDNA). All these changes may predispose individuals to develop age-related diseases earlier in life, particularly cardiovascular diseases and cancer. In addition to this, disproportionate telomere shortening and long-term oxidative stress bring the cell cycle to a stop, i.e. the cells, and thus the body as a whole, age earlier (Regulski 2017). Although senescent cells help to suppress tumour growth in the body during our lives, their accumulation at a later age can cause premature ageing and the development of pathologies (Regulski 2017). Many scientists consider oxidative stress, along with an inflammatory reaction, to be the central mechanism of the complex effect of the air pollution on health and aging (Kunzli and Tager 2005; Lim and Thurston 2019).

Oxidative stress is the imbalance between the production of reactive oxygen species (ROS) (free radicals) and the body's ability to break down and detoxify reaction intermediates (Alfaro-Moreno et al. 2010). Free radicals occur as by-products of oxygenation and metabolism, the formation of which is, among other things, significantly influenced by stress and a number of environmental factors, also including exposure to air pollution (Halliwell and Gutteridge 2015; Deng et al. 2019). Free radicals can affect DNA by degrading its bases, single/double-strand breaks, as well as by the formation of a purine, pyrimidine or saccharide bond, mutations, deletions or translocations and cross-linking with proteins (Lim and Thurston 2019). DNA damage and other biological effects may be caused directly by ROS induced by the stimulation of particulate matter or indirectly through pro-inflammatory mediators released from macrophages (González-Flecha 2004). DNA modifications contribute to the formation of carcinogenesis, the development of chronic non-communicable diseases and also exacerbate aging (Birben et al. 2012). Oxygen radicals may also induce the expression of certain genes involved in signal transduction (Valko et al. 2006). Impact of prenatal exposure is expected too, an increased oxidative DNA damage and lipid oxidation have been found in new-born babies of mothers living in polluted areas (Ambroz et al. 2016).

The effect of exposure may be positive, negative, or hormetic. Hormesis is the term for the phenomenon where, up to a certain point, low exposure has a positive effect on the body, while the effect becomes negative from a certain point. This means that in the short-term specific molecular parameters may improve, for example, the telomere may become longer for a time, or the activity of certain antioxidant enzymes may increase (Gurgueira et al. 2002; Dioni et al. 2011; Hou et al. 2012; Rossnerova et al. 2017). Generally, upon long-term exposure to low doses of pollutants the body develops an adaptive response, meaning that exposure does not cause as much damage in the body as if the body had been exposed to the same concentration suddenly.

The aim of this article is to provide an overview of current knowledge about the impact of air pollution on health, especially at the molecular level, where the basis for the development of the age-related diseases is formed.

Methods

In this narrative review was searched for studies provided explanations of associations between air pollution and its health impact focusing on a molecular level. The PubMed system was used to search for the study results. The search strategy combined terms related to outdoor air pollution/ambient air pollution/pollutants/particulate matter/traffic pollution with outcomes such as aging, biomarkers, oxidative stress, inflammatory reaction, telomere length, telomere shortening, gene expression, microRNA, copy number variation, mitochondrial DNA, cellular senescence, cardiovascular diseases and cancer. Additionally, we searched for the associations between molecular changes (telomere shortening, oxidative stress, …) and development of cardiovascular diseases or cancer, earlier aging, shorter life expectancy. Approximately 220 articles matched our search criteria, 80 articles were referenced. The main criterion for inclusion was the date of publication after 2010. Some older studies have been used to quote consistent

knowledge or definitions. We excluded studies providing ambiguous results or unclear exposure conditions.

Results

The effect of polluted air on mean telomere length

Telomeres are the end parts of eukaryotic chromosomes, which protect their stability and the overall integrity of DNA against loss of genetic information (Blackburn 1991). During a life, i.e. as the number of cell divisions increases, these telomeres gradually get shorter. Therefore, telomere length tends to be referred to as a marker of cell aging or cellular 'senescence' (Levy et al. 1992; Robin et al. 2014; Bernadotte et al. 2016). Changes in telomere lengths and related telomerase activity may be affected by oxidative stress and inflammatory processes induced by environmental factors (Von Zglinicki 2002).

Researchers such as Martens and Nawrot (2016) have closely studied the mechanism of the way polluted air affects cellular senescence, including shortening of the telomere length. Their results showed, that oxidative stress mediated by exposure to dust particles in the air may result both from direct contact with reactive oxygen substances on the surface of particles in the lungs and also through soluble compounds, such as transition metals and organic compounds that have penetrated into the bloodstream, or also from the activation of inflammatory cells generating reactive oxygen and nitrogen. The GGG triplets on telomeres are highly sensitive to hydroxyl radicals and oxidative stress may be the main cause of telomere shortening independently of shortening due to incomplete replication. Accelerated telomere shortening is associated with chronic non-communicable diseases (world´s biggest killer) to develop earlier, particularly cardiovascular diseases and neoplasms, when the strongest link was found in cancers of the bladder, oesophagus, stomach and kidney (Wentzensen et al. 2011; Haycock et al. 2014).

Results from the epidemiological studies concerning telomere length alteration after exposure to indoor and ambient air pollution are shown in Table 1. A cross-sectional study on a group of traffic officers in the centre of Milan showed a significantly shorter mean telomere length in comparison to the control group, which was attributed to increased exposure to traffic pollutants such as benzene (Hoxha et al. 2009). Similar results were shown in a study on coke oven workers exposed to PAHs in Henan, China (Duan et al. 2019). Opposite results were presented in a study from Beijing, where the telomere length mean was significantly higher in truck drivers than in office workers (Hou et al. 2012). In another study from Belgium, an increase in the average annual concentration of $PM_{2.5}$ was associated with the relative shortening of mean telomere length by 17% in the population studied (Pieters et al. 2016).

Telomere length is also affected by prenatal exposure to polluted air. A cohort study of twins in Belgium showed that the placental telomere length is longer in mothers living in areas with lower levels of traffic pollution (Bijnens et al. 2015). Exposure to environmental factors in childhood and adolescence has a far greater impact than exposure in adulthood. The same study of twins showed that telomere length in adulthood correlated more with the level of exposure at birth and at a young age rather than with the level of exposure in adulthood (Bijnens et al. 2017). Other studies have also shown that mothers exposed to higher average PM_{10} and $PM_{2.5}$ concentrations during pregnancy gave birth to children with a shortened length of leukocyte telomeres in the umbilical cord blood and the placental tissue, which may predispose such individuals to environmental factors during later life (Martens et al. 2017; Iodice et al. 2018). In a birth cohort study in China was additionally found that inverse relationships between maternal exposures to air pollutants and cord blood telomere length were more evident in male infants (Song et al. 2019).

Increased telomerase enzyme activity may be explained by the assumption, that short-term exposure to fine particles may temporarily lengthen telomere length in an effort to compensate for loss of part of the DNA molecules (Dioni et al. 2011; Hou et al. 2012). A temporary increase in

Table 1. Summary of associations between air pollution exposure and telomere length.

Author	Study population and design	Pollutant	Exposure data, concentration	Exposure related to result	Result
Bijnens et al. 2015	211 twins, a prospective twin survey (Belgium)	-	Traffic indicators Land use indicators	Doubling of distance to major road (maternal exposure)	↑ 5.32% (95% CI: 1.90–8.8, p = 0.003) in placental TL
Dioni et al. 2011	63 steel workers, a repeated-measure study (Italy)	PM_{10}	3-days mean exposure during work 262 ± 272 μg/m^3 *Measured using light-scattering dust analyser.*	Comparison of TL mean between baseline (1.23 ± 0.28) and postexposure state (1.43 ± 0.51; p < 0.001)	
Duan et al. 2019	782 coke oven workers and referents, a repeated-measure study (China)	PAHs	CO workers: 1.12 (0.34,2.14) mg/m^3*year Referents: 0.07 (0.06,0.09) mg/m^3*year *Measured by passive samplers and estimated to cumulative exposure dose for each subject afterwards.*	Comparison of TL mean between coke oven workers 0.75 (0.51–1.08) and referents 1.05 (0.76–1.44) (p < 0.001)	
Hou et al. 2012	120 truck workers and office workers, a repeated-measure study (China)	$PM_{2,5}$	8-hours mean exposure Truck workers: 126.8 ± 68.8 μg/m^3 Office workers: 94.6 ± 64.9 μg/m^3 *Measured by personal monitor.*	↑ in exposure on examination days	↑ 5.2% (95% CI: 1.5–9.1; p = 0.007) in blood TL
		PM_{10}	14-days mean exposure Truck workers: 121.7 ± 17.8 μg/m^3 Office workers 119.9 ± 18.7 μg/m^3 *Measured by local monitoring stations.*	↑ in exposure on examination days ↑ in exposure over the 14 days before the examination	↑ 7.7% (95% CI: 3.7–11.9; p < 0.001) in blood TL ↓ 9.9% (95% CI: 17.6–1.5; p = 0.02) in blood TL
				Comparison of TL mean between truck workers (0.87, 95% CI: 0.74–1.03) and office workers (0.79, 95% CI: 0.67–0.93) (p = 0.001)	
Hoxha et al. 2009	134 traffic officers and office workers, a cross-sectional study (Italy)	benzene	7-hours mean exposure Traffic officers: 31.8 (9.0–315.7) μg/m^3 Office workers: 13.0 (2.0–115.1) μg/m^3 All participants: IQR = 11.2 μg/m^3 *Measured by personal passive samplers.*	↑ in exposure	↓ 6.4% (95% CI: 2.1–10.4; p = 0.004) in blood TL
				Comparison of TL mean between traffic officers (1.10, 95% CI: 1.04–1.16) and office workers (1.27, 95% CI: 1.20–1.35) (p < 0.001)	
				Comparison of TL mean among traffic officers working in high traffic intensity (1.02, 95% CI: 0.96–1.09) and working in low traffic intensity (1.22, 95% CI: 1.13–1.31) (p < 0.001)	
Iodice et al. 2018	199 healthy pregnant women, a cross-sectional study (Italy)	PM_{10}	Mean exposure during pregnancy 10–90 μg/m3 *Measured by monitoring stations.*	↑ 10-μg/m^3 in exposure during the 1st trimester	↓ in blood TL; adjusted GMR = 0.94 (95% CI: 0.88–0.99;)
		$PM_{2,5}$	Mean exposure during pregnancy 7–69 μg/m^3 *Measured by monitoring stations.*	↑ 10-μg/m^3 in exposure during the 1st trimester	no significant association
Martens et al. 2017	641 mother-newborn pairs, a prospective cohort study (Belgium)	$PM_{2.5}$	Mean exposure during pregnancy 13.4 (4.3–32.5) μg/m^3 *Estimated by high-resolution spatial-temporal interpolation model*	↑ 5-μg/m^3 in exposure during the entire pregnancy (maternal exposure)	↓ 8.8% (95% CI: 14.1–3.1) in cord blood TL and ↓ 13.2% (95% CI: 19.3–6.7) in placental TL

(*Continued*)

Table 1. (Continued).

Author	Study population and design	Pollutant	Exposure data, concentration	Exposure related to result	Result
Pieters et al. 2016	166 elderly non-smokers, a cross-sectional study (Belgium)	$PM_{2,5}$	Annual mean exposure 21.1 ± 1.76 μg/m^3 *Estimated for home address using high-resolution spatial-temporal interpolation model*	↑ 5-μg/m^3 in annual concentration	↓ 16.8% (95% CI: 26.0–7.4; p = 0.0005) in blood TL
Song et al. 2019	762 mother-newborn pairs, a cohort study (China)	$PM_{2,5}$	Mean exposure during pregnancy 69.10 ± 20.04 μg/m^3 *Estimated by spatial-temporal land use regression model*	↑ 10-μg/m^3 in exposure during the 3rd trimester	↓ 3.71 (95% CI: 6.06–1.30; p = 0.003) in cord blood TL
		PM_{10}	Mean exposure during pregnancy 135.46 ± 20.03 μg/m^3 *Estimated by spatial-temporal land use regression model*	↑ 10-μg/m^3 in exposure during the 3rd trimester	↓ 3.24 (95% CI: 5.29–1.14; p = 0.003) in cord blood TL

Abbreviations: TL – telomere length; CO – coke oven; GMR – geometric mean ratio

telomere length might be also caused by the fact that exposure to a polluted environment has been associated with an acute inflammatory reaction in the body and have been resulted in the migration of less mature leukocytes from the bone marrow, characterised by longer telomeres (Dioni et al. 2011). A study on a sample of Italian steelworks employees showed that after three working days the mean telomere length had significantly increased by approximately 16% compared to the length at the start of the working week (Dioni et al. 2011).

The effect of polluted air on miRNA

miRNA are single-stranded small non-coding RNAs of approximately 21–22 nucleotides. They arise from transcription from genes in DNA, and are not subsequently translated into protein. They play a key role in regulating the progression of the cell-division cycle (gene expression), apoptosis and differentiation. miRNAs are named using the prefix 'miR' with a unique identification number (such as miR-1, miR-2) (Tsamou et al. 2018). Certain miRNAs are considered key regulators during cellular senescence. A lower or higher expression of a particular miRNAs during aging may cause the cell-division cycle to stop. The link between miRNAs and aging has not yet been fully clarified, but it is assumed that they play a potential role in aging and age-related diseases (Xu and Tahara 2013).

A number of miRNAs are also associated with exposure to polluted air. Increased exposure to air pollutants has been observed to either increase or decrease the level of gene expression (Tumolo et al. 2020). Although such exposure is associated with an increased rate of morbidity and mortality in a range of chronic non-communicable diseases and the effects on human health seem clear, the mechanisms by which pollutants modify gene expressions have still not been completely clarified (Krauskopf et al. 2018; Tsamou et al. 2018). MiRNAs play an important role in the activation of adaptation mechanisms upon exposure to environmental factors. Defensive and protective mechanisms are triggered in the first phase of adaptation, while carcinogenesis does not develop until after years of long-term exposure (Izzotti and Pulliero 2014).

Various studies have assessed the impact of exposure to particulate matter, metals, PAHs, sulphates, nitrogen dioxide and benzene to the (candidate) functions of miRNAs, resulting in altered miRNAs profile (Vrijens et al. 2015; Krauskopf et al. 2018; Tsamou et al. 2018). The strongest associations upon exposure to particulate matter were observed for $PM_{2.5}$ (Bollati et al. 2010; Fossati et al. 2014; Chen et al. 2018; Krauskopf et al. 2018; Tsamou et al. 2018). Other associations were also observed with PM_{10}, NO_2, SO_4^{2-}, PAHs and metals – miRNA expression was found to be negatively associated with aluminum, antimony, lead, and titanium, and positively associated with molybdenum and tin (Fossati et al. 2014; Motta et al. 2016; He et al. 2018; Krauskopf et al. 2018; Tsamou et al. 2018; Deng et al. 2019).

An overview of the individual miRNAs with dysregulation caused by polluted air is given in the Table 2. Exposure to contaminated particles in association with increased or reduced levels of certain miRNAs may be related with tumours of the breast, prostate, thyroid and brain, but also atherosclerosis and Huntington's disease (Vrijens et al. 2015).

It is essential to seek early diagnostic biomarkers to detect the impact of air pollutants on the health of the population. There is excessive potential for the use of miRNAs as new biomarkers to assess the environmental health risk (Vrijens et al. 2015; Wei et al. 2015; Fenga et al. 2016; Krauskopf et al. 2018; Tsamou et al. 2018). Moreover, some results suggest that PAHs taken by particulate matter can decrease cardiovascular-related gene expression through upregulating miRNA, thus miRNAs may be a new target for therapy of cardiovascular diseases in the future (He et al. 2018).

Table 2. Summary of associations between air pollution exposure and miRNA expression.

Author	Study population and design	Pollutant	Exposure data, concentration	Exposure related to result	Result
Bai et al. 2014	paint sprayers and office workers, a cross-sectional study (China)	Benzene	Chronic occupational benzene poisoning *Chronic benzene poisoning was diagnosed according to diagnostic criteria and principles of occupational benzene poisoning (GBZ 68–2008).*	Comparison of chronic poisoning patients with controls	↑ miR-34a, miR-205, miR-10b, let-7d, miR-185, miR-423-5p-2 ↓ miR-133a, miR-543, hsa-miR-130a, miR-27b, miR-223, miR-142-5p, miR-320b
Bollati et al. 2010	63 steel workers, a repeated-measure study (Italy)	PM_1 PM_{10} metals	3-days mean exposure during work *Measured by light-scattering dust analyser.*	Comparison of postexposure state with baseline	↑ miR-222 (p = 0.002), miR-21 (p = 0.05)
			3-days mean exposure during work *Measured by inductively coupled plasma mass spectrometer.*	↑ in lead exposure ↑ in cadmium exposure	↑ miR-222 (p = 0.02) ↓ miR-146a (p = 0.008) ↓ miR-146a (p = 0.019)
Chen et al. 2018	55 young adult students, a randomized crossover study (China)	$PM_{2,5}$	14-days mean exposure Sham-purified air: 46.8 μg/m^3 True-purified air: 8.6 μg/m^3 Total IQR = 28 μg/m^3 *Measured by personal monitor (indoor) and environmental dust monitor (outdoor).*	Comparison of the true purification intervention with the sham ↑ IQR in exposure	↑ miR-21-5p (p = 0.002), miR-187-3p (p = 0.002), miR-146a-5p (p = 0.006), miR-199a-5p (p = 0.001), miR-1-3p (p = 0.006) ↓ miR-21-5p (p = < 0.001), miR-1-3p (p = 0.005), miR-187-3p (p = 0.028), miR-146a-5p (p = 0.012),
Deng et al. 2019	360 healthy male coke oven workers, a repeated-measure study (China)	metals	*Measured in urine by plasma-mass spectrometry and gas chromatography–mass spectrometry.*	↑ in exposure to: aluminum, antimony, lead, titanium ↑ in exposure to: molybdenum, tin	↓ miR-16-5p, miR-320b, miR-27a-3p, let-7b-5p, miR-126-3p, miR-142-5p, miR-150-5p, miR-24-3p, miR-28-5p, ↑ miR-126-3p, miR-28-5p, let-7b-5p, miR-24-3p, miR-27a-3p, miR-320b, miR-16-5p, miR-451a
Fossati et al. 2014	153 elderly males, a longitudinal cohort study (USA)	$PM_{2,5}$	7-days mean exposure IQR = 3,83 μg/m^3 *Measured by monitoring stations (the median distance from participants residence to monitor site was 24 km).*	↑ IQR in exposure	↓ miR-1, miR-126, miR-135a, miR-146a, miR-155, miR-21, miR-222, miR-9
		SO_4^{2-}	48-hours mean exposure IQR = 1.47 μg/m^3 *Measured by monitoring stations.*	↑ IQR in exposure	↓ miR-1, miR-146a, miR-21, miR-126, miR-135a, miR-155, miR-222, miR-9
He et al. 2018	Experimental study on human umbilical cord vein cells (China)	PAHs	Concentrations 0, 100, 200, 300, 400, and 500 μg/ml of PAHs particle solutions were added to the culture medium for 24 h before assays.	Changes in PAHs-treated sample	↑ miR-3613-5p, miR-376 c-5p, miR-376b-5p, miR-652-5p, miR-3648, miR-7641, miR-98-3p, miR-4485, miR-585-3p, miR-31-3p, miR-299-5p, miR-3917, miR-155-3p ↓ – miR-99b-3p, miR-532-5p

(*Continued*)

Table 2. (Continued).

Author	Study population and design	Pollutant	Exposure data, concentration	Exposure related to result	Result
Krauskopf et al. 2018	24 non-smokers, experimental cross-over study (United Kingdom)	$PM_{2,5}$	2-hours mean exposure Polluted area: 25.6 (21–30.2) μg/m^3 Traffic-free area: 5.6 (4.5–6.8) μg/m^3 *Measured by real-time condensation particle counter.*	Comparison of postexposure state with baseline	↓ miR-133a-3p, miR-193b-3p, miR-433-3p, miR-145-5p, miR-27a-5p, miR-580-3p, miR-6716-3p ↑ miR-1224-5p, miR-3127-5p
		PM_{10}	2-hours mean exposure Polluted area: 37.0 (32.2–41.7) μg/m^3 Traffic-free area: 16.0 (12.5–19.5) μg/m^3 *Measured by real-time condensation particle counter.*		
Motta et al. 2016	90 obese individuals, a cross-sectional study (Italy)	PM_{10}	Daily mean exposure 48 h before the recruitment day *Estimated for home address using spatial-temporal interpolation model.*	↑ 1-μg/m^3 in exposure	↓ miR-26a (p = 0.012), miR-101 (p = 0.028), miR-145 (p = 0.001), miR-197 (p = 0.008), miR-30b (p = 0.009), miR-345 (p = 0.009), miR-425–5p (p = 0.017), miR-331 (p = 0.022), miR-140–3p (p = 0.023)
Tsamou et al. 2018	210 mother-newborn pairs, a birth cohort study (Belgium)	$PM_{2,5}$	Mean exposure during pregnancy Trimester 1: 15.99 ± 5.29 μg/m^3	↑ 5-μg/m^3 in exposure during the 1st trimester	↑ miR-20a (p = 0.007), miR-21 (p = 0.015)
			Trimester 2: 16.38 ± 5.06 μg/m^3 *Estimated for home address using spatial-temporal interpolation model.*	↑ 5-μg/m^3 in exposure during the 2nd trimester	↓ miR-16 (p = 0.069), miR-20a (p = 0.052), miR-21 (p = 0.022), miR-146a (p = 0.012), miR-222 (p = 0.034)
		NO_2	Mean exposure during pregnancy Trimester 1: 19.97 ± 5.86 μg/m^3	↑ 5-μg/m^3 in exposure during the 1st trimester	↑ miR-21 (p = 0.076)
			Trimester 2: 20.69 ± 6.04 μg/m^3 *Estimated for home address using spatial-temporal interpolation model.*	↑ 5-μg/m^3 in exposure during the 2nd trimester	↓ miR-20a (p = 0.058), miR-21 (p = 0.042), miR-146a (p = 0.072)

Abbreviations: PAHs – polycyclic aromatic hydrocarbons; IQR – interquartile range

The effect of polluted air on changes in copy number variations in mitochondrial DNA

Copy number variation (CNV) is a state where parts of the genome are repeated. This is a type of genomic structural variation, involving both deletion (loss of part of the genome) or duplication (the duplication of part of the genome) (Freeman 2006). The deletion and duplication of chromosomal segments are the main source of variation among individual people and are also a basic factor in human evolution and many diseases (mental, development, cancer). CNV occur faster than other types of mutation, owing to specific mechanisms. There are two theories concerning the contemporary molecular mechanisms that probably relate to these variations. CNV are produced by homologous recombination between repeated sequences or by non-homologous recombination mechanisms occurring in the whole genome (non-repeating CNV) (Freeman 2006; Montavon et al. 2012).

Mitochondria are one of the main cellular targets of environmental pollutants, which can damage mitochondrial morphology, function and DNA, which is reflected in the mtDNA copy number, as is a marker for oxidative damage and mitochondrial failure (Hou et al. 2013; Boovarahan and Kurian 2018). So far, few studies have focused on the link between mtDNA copy number variation and aging. Even so, it is clear that certain types of mtDNA copy number variations are probably linked with cellular senescence and the development of various multiple diseases (e. g. cancer or schizophrenia) (Iakoubov et al. 2013).

Some studies have shown that mtDNA copy number is associated with a polluted environment (Table 3). A Chinese study analysed a group of truck drivers and a group of office workers. The researchers determined how mtDNA is affected by exposure to PM particles and elemental carbon. There was a lower number of mtDNA copies observed in all participants with higher personal exposure to elemental carbon and exposure to ambient PM_{10}, while no associations were observed with exposure to $PM_{2.5}$ (Hou et al. 2013). Other Chinese study on coke oven workers showed that exposure to PAHs was associated with lower mtDNA copy number variation compared to the control group (Duan et al. 2020). One study on a sample of older men showed that exposure to substances containing carbon, expressed as black carbon (BC), which are an indicator of traffic pollution, was associated with increased blood pressure (BP) and a higher mtDNA copy number (Zhong et al. 2016). Another study focused on women during pregnancy and the association between exposure to particulate matter and fetal development disorders, birth problems, probably due to the presence of oxidative stress and systemic inflammation; the oxidative stress biomarker used was mtDNA measures. The study showed that exposure to particulate matter was associated with a higher mtDNA copy number. Increased fetal heart rate and reduced birth weight have been positively associated with exposure to higher concentrations of PM_{10} (Iodice et al. 2018). However, very few studies about the impact of air pollution on mtDNA measures have yet been conducted, so the results are inconsistent. Nevertheless, the number of mtDNA copies could be considered as a potential biomarker for mitochondrial damage and dysfunction (Carugno et al. 2012).

The effect of polluted air on the development of diseases

The primary effect of particulate matter occurs at the point it enters the body, i.e. in the lungs. A series of cells are activated in the lungs (such as macrophages, epithelial cells, and dendritic cells), which may lead to local inflammation. Cytokines are also produced, that may have a local as well as a systemic effect. Another mechanism of the effect of particulate matter is translocation beyond the epithelial barrier, by means of dendritic cells or epithelial transport, which may subsequently affect the vascular system (Alfaro-Moreno et al. 2010). A number of studies have demonstrated that particles penetrate directly into the bloodstream and then on to outlying organs (Nemmar et al. 2002; Brook et al. 2004). Nemmar et al. (2002) have performed experimental studies in volunteers, who inhaled carbon particles <100 nm in diameter coupled with radioactive technetium. The results showed that the radioactivity was present in the blood between 1 and 60 minutes after inhalation,

Table 3. Summary of associations between air pollution exposure and mitochondrial DNA copy number.

Author	Study population and design	Pollutant	Exposure data, concentration	Exposure related to result	Result
Carugno et al. 2012	519 occupational individuals and referents, a cross-sectional study (Italy)	Benzene	Mean exposure during work shifts Referents: GM = 7.7 μg/m^3 Exposed participants: GM = 37.7 μg/m^3 *Measured by personal passive samplers.*	↑ IQR increase in exposure Comparison of benzene-exposed participants with referents: ↑ ($p < 0.05$) in mtDNA	↑ 10.3% (95% CI: 5.4–15.5; $p < 0.001$) in mtDNA
Duan et al. 2020	782 coke oven workers and referents, a repeated-measure study (China)	PAHs	CO workers: 1.12 (0.34,2.14) mg/m^3*year Referents: 0.07 (0.06,0.09) mg/m^3*year *Measured by passive samplers and then estimated to cumulative exposure dose for each subject.*	Comparison of the mtDNA in exposure group (0.60 ± 0.29) and in the control group (1.03 ± 0.31) ($p < 0.001$)	
Hou et al. 2013	120 truck drivers and office workers, a repeated-measure study (China)	$PM_{2,5}$	8-hours mean exposure during work Truck workers: 126.8 ± 68.8 μg/m^3 Office workers: 94.6 ± 64.9 μg/m^3 *Measured by personal monitors.*	no significant association	
		PM_{10}	8-days mean ambient exposure Total mean: 120,6 ± 18.3 μg/m^3 *Measured by local monitoring stations.*	↑ 10-μg/m^3 in exposure before the examination day	↓ 0.008 (95% CI: 0.043–0.008, $p = 0.004$) in mtDNA
		EC	8-hours mean exposure during work Truck workers: 17.2 ± 6.6 μg/m^3 Office workers: 13.0 ± 4.0 μg/m^3 *Measured by personal monitors.*	↑ in personal exposure	↓ 0.059 (95% CI:0.011–0.0006, $p = 0.03$) in mtDNA
Iodice et al. 2018	199 healthy pregnant women, a cross-sectional study (Italy)	PM_{10}	Mean exposure during pregnancy 10–90 μg/m3 *Measured by monitoring stations.*	↑ 10-μg/m^3 in exposure during the 1st trimester	↑ 1.14 (95% CI: 1.08–1.20, $p < 0.001$) in mtDNA
		$PM_{2,5}$	Mean exposure during pregnancy 7–69 μg/m^3 *Measured by monitoring stations.*	↑ 10-μg/m^3 in exposure during the 1st trimester	↑ (not significant) in mtDNA
Pieters et al. 2016	166 elderly nonsmokers, a cross-sectional study (Belgium)	$PM_{2,5}$	Annual mean exposure 21.1 ± 1.76 μg/m3 *Estimated for home address using high-resolution spatial-temporal interpolation model.*	↑ 5-μg/m^3 in annual concentration	↓ 25.7% (95% CI: 35.2–16.2, $p < 0.0001$) in mtDNA
Zhong et al. 2016	675 older men, a prospective cohort (USA)	BC	28-days mean exposure 1,02 μg/m^3 *Measured by stationary monitor.*	↑ in exposure	↑ 0.12 SD (95% CI:0.03–0.20; $p = 0.007$) in mtDNA/nDNA

Abbreviations: PAHs – polycyclic aromatic hydrocarbons; IQR – interquartile range; SD – standard deviation; nDNA – nuclear DNA; mtDNA – mitochondrial DNA; GM – geometric mean; BC – black carbon; EC – elemental carbon

supporting the theory that the inhaled particles are translocated from the lungs to the bloodstream. An association were also found between polluted air and metabolic dysfunction resulting in the development of diabetes (Lim and Thurston 2019).

Molecular mechanisms of the effect of polluted air on the development of cardiovascular diseases

It is known that cardiovascular diseases are caused by many factors. Polluted air plays a role in the development of cardiovascular diseases as both a direct and an indirect mechanism. Oxidative stress and chronic inflammation caused by the mechanical action of particulate matter subsequently results in a systemic effect, which also has an impact on cardiac function. Oxidative stress and inflammation damage in the platelets, blood vessels and myocardium, cause changes in blood coagulation, thus promoting the development of atherosclerosis and, in the short-term, causing plaque instability (atheromas) and vasoconstriction, that might lead to arrhythmia and sudden cardiac events or strokes (Brook et al. 2004; Mills et al. 2009). Air pollution also plays a direct role in the development of cardiovascular diseases, upon the translocation of dust particles from the lungs into the bloodstream with a consequent direct toxic effect and resulting in oxidative stress and inflammation in other organs (Nemmar et al. 2002; Mills et al. 2009). Obviously, people already suffering from some form of co-morbidity, such as hypertension or diabetes, are more sensitive to the effects of polluted air (Nemmar et al. 2013).

Studies focusing on exposure in animals and people to diesel exhaust fumes, which are a rich source of fine and ultra-fine particles, show the significant changes in blood pressure, heart rate, vascular tone, endothelial function, myocardial perfusion, the risk of thrombosis, atherogenesis and plaque stability. Oxidative stress was manifested as a pathobiological mechanism, whereby inhalation of diesel exhaust fumes results in the development of cardiovascular dysfunction (Wilson et al. 2018). Positive correlations have been observed between the level of one of the main antioxidant enzymes – glutathione peroxidase and survival time with no cardiovascular events (Blankenberg et al. 2003). $PM_{2.5}$ particles have a toxic effect directly on myocardial cells. Researchers from China have studied this influence in detail and found that $PM_{2.5}$ exposure affected the expression of nearly 500 genes compared to the control group (Feng et al. 2017). At the same time, increased regulation has been observed in cellular processes, such as immune response, cell maturation, embryonic heart tube morphogenesis, cellular response to electrical stimuli and the regeneration of skeletal muscle tissue. In contrast, reduced regulation has been observed in transcription, rhythmic processes, apoptosis protein destabilization and innate immune responses. A number of signal pathway regulations were also affected (Feng et al. 2017).

Attempts have been made by Nemmar et al. (2013) to explain the pathophysiological mechanism of the action of polluted air on the incidence of cardiovascular diseases. Exposure to polluted air is associated with rapid changes in the balance of the autonomic nervous system with sympathetic activation to the detriment parasympathetic activation, resulting in changes in respiration, heart rate and heart rate variability. These factors may pose a risk of sudden cardiac death. Sympathetic activation is caused, amongst other factors, by the direct effect of pollutants on the ion channels in the heart (Seaton and Donaldson 2005).

The ultimate impact of polluted air on increased morbidity and mortality to cardiovascular diseases is then corroborated by the results from a series of major studies. A study conducted in the USA on a sample of 0.5 million people showed that increased exposure to $PM_{2.5}$ of 10 $\mu g/m^3$ was associated with a 16% arise in the mortality rate caused by ischemic heart disease and a 14% increase in the stroke fatality rate (Hayes et al. 2019).

Molecular mechanisms of the effect of polluted air on the development of cancer

Polluted air consists of a complex mixture of gases and solids (PM). The majority of published studies have confirmed that these substances play an important role in subsequent adverse effects on the human body (Lewtas 2007; Nemmar et al. 2013). A number of gaseous substances and solid particles are a significant source of exposure to mutagenic and carcinogenic chemicals, which may cause oxidative damage and damage to DNA (chronic effects), that may lead to the development of carcinogenesis, amongst other things. Studies focusing on short-term and long-term exposure to polluted air are associated with a degree of genetic damage. Long-term epidemiological studies indicate a higher risk of developing cancer, particularly lung cancer, and also an increased risk of death from this disease through the effects of exposure (Lewtas 2007; Nemmar et al. 2013).

Exposure to individual particles in the air induces an inflammatory response in the human body (Lewtas 2007). The biggest role is played by $PM_{0.1}$ and $PM_{2.5}$. Ultra-fine fractions exhibit greater toxicity at the same mass concentrations compared to larger particles, owing to increased reactivity, surface area and thus a greater number of particles. However, other studies have proven that even PM_{10} may play a role in the development of cancer through mechanisms such as damage to epithelial cells in the lungs, the effects of cell proliferation including cytotoxicity, the release of inflammatory mediators (chemokines, cytokines), changes in gene expression by binding to a receptor (certain changes in phenotypes could increase the likelihood of cancer cells developing) and various forms of cellular DNA damage, including epigenetic changes. It is possible that exposure to such particles could also affect the later stages of cancer development, such as chromosomal instability and cell migration, which are an important part of the propagation of tumours and metastases (Nemmar et al. 2013).

Formed labile DNA adducts are often associated with a high ability to create a gene mutation, which is considered a particularly important factor in the initiation of the cancer development phase (Nemmar et al. 2013). This has been proved for several polycyclic aromatic hydrocarbons (including a strong carcinogens, e.g. benzo[a]pyrene, dibenzo[a,l]pyrene) and benzene. These aromatic compounds are metabolised to phenols, oxidized to catechols and then to quinines. Quinones react with DNA to produce depurinating adducts that cause apurinic sites and induce A number of studies have been devoted to associations between polluted air and cancer in general. A study conducted on almost 900 thousand people aged 40–89, with the individual people being allocated places of residence and individual annual average concentrations of PM_{10}, $PM_{2.5}$, NO_2, O_3 and SO_2 particles, showed a positive association between exposure and mortality due to cancer for all pollutants with the exception of ozone (Carey et al. 2013).

Several studies have explored the association between air pollution and the risk of lung cancer (LC). Most of these studies have confirmed a positive association between exposure to pollutants and the risk of developing LC (Raaschou-Nielsen et al. 2011; Carey et al. 2013; Chen et al. 2015). At the same time, the risk of lung cancer has been shown to be considerably lower in people living in areas with a low population density, and therefore lower traffic density (Meijer et al. 2012). These studies support the idea that the risk of LC is linked to exposure to air pollution associated with traffic and one's place of residence. However, this is opposed by other European study, where residence near roads was the indicator for monitoring individuals. The pollutants (NO_2, PM_{10}, SO_2) were assessed using concentrations of data from monitoring stations in routine monitoring of air quality and the study found no significant associations between the development of LC and living in the vicinity of major roads (Vineis et al. 2006). Another cohort study from Canada found no association between the incident of lung cancer and exposure of ambient ultrafine particles (Weichenthal et al. 2017).

Breast cancer is the most frequently diagnosed cancer in the majority of European women. Certain factors are known to increase the risk of this cancer, including hormonal, nutritional and environmental factors, as well as genetic factors (the most important genes BRCA1/BRCA2). One risk factor already mentioned above is the environment in which we live and its associated polluted air. This is a mixture of chemicals containing carcinogenic

compounds and substances with endocrine-disrupting properties. It may also result in the development of gene sequence variants (Homaei Shandiz and Hadizadeh Talasaz 2017). Fine particles in the air can promote inflammation or densify breast tissue, and for these reasons exposed women may be more susceptible developing tumours. Women with dense breast tissue are several times more likely to develop some form of breast cancer (Villeneuve et al. 2018). Studies conducted in Canada, Denmark and the USA, for instance, have found that women living in urban areas with high levels of air pollution have as much as a 30% higher risk of developing breast cancer than women living in rural areas. A positive link was also found between premenopausal breast cancer and $PM_{2.5}$ exposure and a postmenopausal breast cancer and exposure to NO_2 (Meijer et al. 2012; Homaei Shandiz and Hadizadeh Talasaz 2017; Schmidt 2018; Villeneuve et al. 2018; White et al. 2018). But Spanish cohort Sister Study found no association between ambient air pollution and breast cancer risk (Reding et al. 2015).

Prostate cancer (PC) is one of the most frequently diagnosed forms of cancer in males. However, its etiology is still, to a considerable extent, unclear. According to various studies, risk factors include ethnicity, age, genetics, hormonal factors, nutrition, but also environmental factors. The effect of polluted air on PC is still being researched. A series of studies have focused on mortality caused by PC in association to where such individuals live. Studies on various different populations have shown that men living in polluted area show a higher incidence of PC compared to those living in unpolluted area (Ramis et al. 2011; Parent et al. 2013; Pouresmaeili et al. 2015). It is not only where these men live in the vicinity of heavy traffic that is studied in association with the incidence of cancer, but also the amount of greenery in the area. Men living in greener areas have a lower risk of developing PC, regardless of socio-demographic and lifestyle factors; however, these observations require further confirmation (Demoury et al. 2017). In opposition to this, there is a study from Denmark, focusing of the incidence of PC in men aged 50–83, in which low population density had no influence on the incidence of PC (Meijer et al. 2012).

A study exploring the risk of kidney cancer (KC) in professional groups working in a dusty environment containing petrol, engine fumes, polycyclic aromatic hydrocarbons and other substances found a significantly higher incidence of KC in relation to PM concentrations (Raaschou-Nielson et al. 2017). Another study has observed a positive association between the occurrence of kidney cancer and $PM_{2.5}$ concentrations (Turner et al. 2017). The same study also presented a positive association between exposure to $PM_{2.5}$ particles and the development of bladder cancer, and also between NO_2 exposure and colorectal cancer (Turner et al. 2017).

Discussion

Epidemiological studies on the relationship between air pollution and health consequences are methodologically critical. In general, it is difficult to identify the factors that cause chronic non-communicable diseases. Despite the numerous correlations between polluted air and higher disease and mortality risk, there are still concerns related to the long-term chronic impact of air pollution on morbidity and mortality. The effect of polluted air is often considerably higher in people suffering for some comorbidity and therefore, mortality increases rather with higher short-term air pollution.

The epidemiological studies considering the effect of air pollution on health are not always precisely defined, especially related to exposure conditions. An overview of exposure characteristics and results of referenced studies are presented in the tables above (see Table 1–3). Methods of exposure estimation have not been unified yet, therefore the results of various studies may often be incomparable. Some researchers present results related to hourly or daily exposure and some results are presented completely without exposure concentration, for example, using traffic and landscape indicators (Bijnens et al. 2015). When discussing the long-term impact of the polluted air, it is crucial to know annual mean of pollutants in the area of interest. Moreover, the difference in

exposure between control and exposure group is not sometimes remarkable (especially in ambient air) (Hou et al. 2012, 2013). Furthermore, exposure concentration is often given with a large standard deviation/confidence interval, if it is mentioned at all (Hoxha et al. 2009; Dioni et al. 2011; Hou et al. 2012, 2013; Iodice et al. 2018). In addition, the results of short-term exposures should be interpreted with caution. For example, the results of acute high exposure to pollution and telomere lengthening may be questionable (Hou et al. 2012). This could give the false impression that telomere length in individuals is not stable, and therefore, it is not an appropriate indicator of body condition/biological age.

Studying the association between above-mentioned molecular changes and polluted air is a relatively new direction in research. In order to enable results to be compared, it would be advisable to create standards for exposure estimation modelling, as well as for epidemiological studies in the real environment. Further research should focus on studying how the body adapts to a polluted environment. Although this issue has not been fully explored yet, it is clear that an adapted body has a different response than an unadapted organism and some of these adaptation mechanisms could be hereditary. It is known, that children born to mothers exposed to pollution show detectable changes at the molecular level at birth. Based on this assumption, prenatal exposure should always be considered in studies. It is necessary to identify congenital and acquired molecular changes separately. These mechanisms must be properly studied so that human adaptation to external stressors is differentiated from the simple presence of compensation processes. In the short-term, the body is capable of exerting a great compensatory effort, which could temporarily improve certain molecular parameters. Such chronic strain on the body then results in premature aging and a shortened life.

Conclusion

Long-term exposure to polluted air has an effect on a number of changes at the molecular level of the body. The common attribute to all of these is oxidative stress. Its long-term presence in the body can be associated with negative changes, which could contribute to the development of chronic diseases and premature aging. Oxidative stress is directly associated with the shortening of telomere length and with the presence of chronic systemic inflammation. An excessive telomere shortening induces premature aging as well as the development of cardiovascular diseases and cancer. Moreover, exposure to air pollutants induces gene expression, increases or reduces the levels of various miRNAs and also affects mtDNA copy numbers, which may lead to illness. These impacts may be prevented by reducing exposure to polluted air. It is known that the overall reduction of air pollution (transport aspects, limit values, moderate of energetics, etc.) is the main solution to protect the population from health impacts. However, reducing air pollution is an ever-topical political, economic and social problem and improving air quality is a slow and complex process. Therefore, it is often more effective to appeal to people to direct on living a healthy lifestyle, which undoubtedly supports healthy aging. For example, moving to less polluted areas or at least away from major roads could increases a person's chance of longer and healthier life; or higher antioxidant intake in diet may also compensates the harmful effect of exposure. It is necessary to continue exploring the association between the long-term exposure to air pollution and changes at the molecular level. At the same time, it is important to focus on the consistent determination of exposures in research.

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