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Increased telomere length and mtDNA copy number induced by multi-walled carbon nanotube exposure in the workplace

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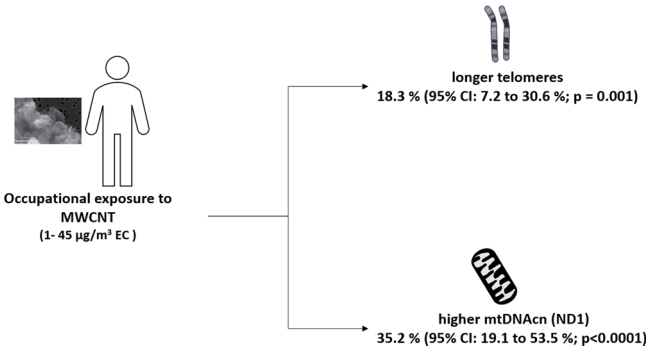
GRAPHICAL ABSTRACT



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ABSTRACT

Carbon nanotubes (CNTs) except MWCNT-7 have been classified as Group 3 ["*Not classifiable as to its carcinogenicity to humans*"] by the IARC. Despite considerable mechanistic evidence *in vitro/in vivo*, the classification highlights a general lack of data, especially among humans. In our previous study, we reported epigenetic changes in the MWCNT exposed workers. Here, we evaluated whether MWCNT can also cause alterations in aging related features including relative telomere length (TL) and/or mitochondrial copy number (mtDNAcn). Relative TL and mtDNAcn were measured on extracted DNA from peripheral blood from MWCNT exposed workers ($N = 24$) and non-exposed controls ($N = 43$) using a qPCR method. A higher mtDNAcn and longer TL were observed in MWCNT exposed workers when compared to controls. Independent of age, sex, smoking behavior, alcohol consumption and BMI, MWCNT-exposure was associated with an 18.30 % increase in blood TL (95 % CI: 7.15–30.62 %; p = 0.001) and 35.21 % increase in mtDNAcn (95 % CI: 19.12–53.46 %). Our results suggest that exposure to MWCNT can induce an increase in the mtDNAcn and TL; however, the mechanistic basis or consequence of such change requires further experimental studies.

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1. Introduction

Carbon nanotubes (CNTs) with its specific electrical and thermal properties, and unique mechanical properties, have a great potential for commercialization. On the other hand, there are concerns about its effect on worker/consumer health from exposure during manufacturing/handling and the use of consumer products. Studies thus far have established the toxicity and potential carcinogenicity of several forms of CNTs, in *vitro* and in rodent models. Since no human cancer data are available, the International Agency for Research on Cancer (IARC) focused on these results assessing the mechanism of toxicity and carcinogenicity of single-walled (SWCNT) and multi- walled (MWCNT) carbon nanotubes. Based on these studies, a particular rigid MWCNT, namely Mitsui 7 (MWCNT-7), was classified as *Group 2B* (*possibly carcinogenic to humans*) (IARC working group on the Evaluation of Carcinogenic Risks to Humans, 2017). Other types of CNTs (MWCNT/SWCNT) were categorized into *Group 3*, which means they are not classifiable as to their carcinogenicity to humans. The mechanistic data regarding end-points related to lung cancer and mesothelioma, are too limited to draw conclusions (IARC working group on the Evaluation of Carcinogenic Risks to Humans, 2017).

Only recently, some epidemiological studies, mostly cross sectional in nature, have started providing evidence on the early biological effects of CNT in humans. A cross-sectional study by Beard et al. Beard et al. (2018), conducted in the US in a large group of workers (N = 108), associated elevated blood and sputum biomarkers, like IL-18, fibrinogen, endothelin-1 and different metalloproteinases, with both exposure to CNTs and nanofibres. The conclusion was that inhalable rather than respirable CNTs were more consistently associated with biomarkers of fibrosis, inflammation, oxidative stress. Another study by Fatkhutdinova et al. Fatkhutdinova et al. (2016), revealed an increase in fibrotic markers and inflammatory cytokines, in biofluids of a small group (N = 10) of MWCNT exposed workers compared to controls. In a subsequent study in the same population, Shvedova et al. Shvedova et al. (2016) showed significant changes in expression of several key pathways, reflective of MWCNT-induced toxicity and their potential to trigger pulmonary, cardiovascular, and carcinogenic outcomes in humans. Lee et al. Lee et al. (2015) observed and increase in oxidative stress markers in the exhaled breath condensate of exposed workers (N = 9). These studies support the results from *in vitro* and animal studies, stating that CNT exposure can induce oxidative stress and inflammation.

Vlaanderen et al. Vlaanderen et al. (2017a) conducted a cross-sectional study in a rather small (N = 22), but well characterized group of MWCNT exposed workers compared to controls (N = 39). They observed increase in immune markers including basic fibroblast growth factor, and soluble IL-1 receptor II in MWCNT exposed workers. Based on the same set of workers Kuijpers et al., (Kuijpers et al., 2018) observed an increase in a cardiovascular biomarker (endothelial damage marker intercellular adhesion molecule-1), associated with MWCNT exposure. Furthermore, Ghosh et al. Ghosh et al. (2017) found differences in gene-specific DNA methylation promotor CpGs for different genes, *e.g.* ATM and HDAC4 in the same population.

Mitochondria, being a major source and a target of intracellular reactive oxygen species, mitochondrial DNA (mtDNA) is particularly vulnerable. We estimated mtDNA copy number by measuring the relative levels of unique mtDNA sequences of ND1 (mitochondrial encoded NADH dehydrogenase 1) gene and hmito3 (129-bp fragment) compared to nuclear human β-globin (HBG) gene. Increased mitochondrial biogenesis as an adaptive response to oxidative stress, results in an increase in mtDNA copy number (mtDNAcn; mitochondrial to nuclear genome ratio) (Malik and Czajka, 2013). Since ROS play a key role in the regulation of mtDNAcn (Hori et al., 2009), it serves as a potential biomarker of ROS induced mitochondrial dysfunction (Malik and Czajka, 2013; Janssen et al., 2012; Hou et al., 2010). In addition to mtDNAcn, previous studies have also reported the influence of inflammation and oxidative stress on relative telomere length (TL) (Lee and Wei, 2000; von Zglinicki, 2002; Richter and von Zglinicki, 2007; Jurk et al., 2014). Telomeres consist of tandem repeats of DNA (5′-TTAGGG-3′), which play a critical role in chromosome stability and may be affected by environmental and occupational chemicals (Martens and Nawrot, 2018). Based on previously described evidence that CNT exposure can result in elevated ROS-formation and inflammation, we hypothesize that occupational exposure to MWCNT can influence both mitochondrial function and telomeres, as reflected by the mtDNAcn and TL, respectively.

2. Study design

The present study was designed to study the effect of MWCNT exposure at workplace on telomere length (TL) and mitochondrial copy number (mtDNAcn) in DNA isolated from peripheral whole blood. This section provides a brief overview of the study population and methods used; which has been described elaborately in the Supplementary section “Materials and Methods”. The study was approved by the Commission for Medical Ethics of UZ Leuven (reference number S54607). Workers (N = 24) were recruited from a factory producing MWCNTs commercially and compared to 43 control subjects (no history of MWCNT exposure). Exposure assessment for MWCNT-exposed workers was performed earlier (Vlaanderen et al., 2017b; Kuijpers et al., 2016) and is described in supplementary section “M.1. Study participants and exposure assessment”. Biological sample collection was concluded in 2013, and is previously described by Vlaanderen et al. Vlaanderen et al. (2017a). The demographic characteristics of the study population are summarized in Table 1. mtDNA content (Janssen et al., 2012) and average relative TL (Martens et al., 2016; Cawthon, 2009) was measured using quantitative real-time polymerase chain reaction (qPCR) assay, according to methods previously published and is

Table 1
Demographic characteristics of the study population reported as N, (%) and mean ± SD.

Variables		Control (N = 43)	Exposed (N = 24)	P-value
Sex	Male	32 (74.4 %)	20 (83.3 %)	0.409
	Female	11 (25.6 %)	4 (16.7 %)	
Age (years)		34.6 ± 8.57	35.9 ± 6.90	0.729
BMI (kg/m^2)		24.88 ± 4.71	27.19 ± 4.99	0.064
Smoking	Never smoker	24 (55.8 %)	13 (54.2 %)	0.805
	Former smoker	7 (16.3 %)	6 (25.0 %)	
	Current smoker	12 (27.9 %)	5 (20.8 %)	
Alcohol consumption	Yes/No	35/8	15/9	0.091
	Glasses/day[b]	1.1 ± 0.91	0.9 ± 0.77	
Previous history of exposure to chemicals[a]		9 (20.9 %)	8 (33.3 %)	
Duration of exposure to nanoparticle at current job (years)		/	4.25 ± 2.40	

[a] as reported by the study subjects.
[b] Alcoholic drinks consumed on average per day over the past 4 weeks.

described in supplementary section "M.3. mtDNA copy number and TL assessment by qPCR".

3. Results

3.1. Mitochondrial DNA content

In unadjusted analysis a higher mtDNAcn was observed in MWCNT exposed workers compared to controls (Fig. 1**A and B**). After adjustment for age, sex, smoking behaviour, alcohol consumption and BMI, a 35.2 % (95 % CI: 19.1–53.5 %; $p < 0.0001$) higher mtDNAcn was observed in exposed workers, using the ND1 mitochondrial gene (Table 2). When using the mitochondrial hmito3 gene, exposed workers showed a 37.4 % (95 % CI: -20.6–92.8%; $p = 0.068$) higher mtDNAc compared to non-exposed individuals.

Besides comparing the exposed workers with the non-exposed workers, the association was examined in different groups of exposure (lab low, lab high and operator) compared with the non-exposed controls. In unadjusted (Fig. 2A) and fully adjusted analysis (Table 2), mtDNAcn, evaluated using ND1, showed significant differences between all the groups and the non-exposed controls. A 26.5 % (95 % CI: 6.4–50.7 %; $p = 0.008$) difference was found with the "lab low"-group, a 35.5 % (95 % CI: 10.2–66.3 %; $p = 0.004$) difference with the "lab high"-group and a 40.6 % (95 % CI: 13.8–73.4 %, $p = 0.002$) difference with the "operator"-group when compared to the non-exposed controls. For Hmito3 (Fig. 2B and Table 2), no significant differences were found between the different groups and the non-exposed controls.

3.2. Telomere length

Compared to the non-exposed controls, the MWCNT exposed workers had consistently longer telomeres (Fig. 3A and Table 2). Workers exposed to MWCNT had 18.3 % (95 % CI: 7.2–30.6 %; $p = 0.001$) longer telomeres compared to the non-exposed controls (Table 2). When comparing the different exposure groups (Fig. 3**B and** Table 2), 27.1 % (95 % CI: 10.9–45.5 %; $p = 0.001$) significantly longer telomeres were observed in the "lab low"-group, compared to the non-exposed controls. In addition, longer telomeres were also observed in the "operator"-group when compared to the non-exposed controls (18.9 %; 95 % CI: 1.39–38.99 %; $p = 0.033$). In the "lab high"-group no significant difference in telomere length was observed when compared to the non-exposed controls.

4. Discussion

4.1. MWCNT exposure is associated with an increase in mtDNAcn

The first key finding of the present study is that MWCNT exposure is significantly associated with an increase in mtDNAcn when compared to non-exposed controls. This is in line with the observed increase in oxidative stress and inflammatory response in several studies (Fatkhutdinova et al., 2016; Shvedova et al., 2016), including the ones reported on the present population (Kuijpers et al., 2018; Vlaanderen et al., 2017b). In our study, a positive association between MWCNT exposure levels and mtDNAcn was observed, when comparing three different exposure groups (lab low, lab high and operator) with the non-exposed controls. These associations were independent of the effect of age, sex, smoking behaviour, alcohol consumption and BMI.

Although the biological mechanism by which environmental exposure can induce an increase in mtDNAcn is still to be revealed, a hypothesis is proposed by Lee et al. Lee et al. (2002). Several studies have shown a close association between an increase in mtDNAcn and DNA damage by ROS and reduced respiratory chain function as a result of oxidative damage (Smith et al., 2012; Lee et al., 1998; Fahn et al., 1998; James and Murphy, 2003). As mentioned before, the increase in mtDNAcn is thought to be a compensation for oxidative damage to mtDNA (Malik and Czajka, 2013). Although, whether mtDNAcn has a direct role in carcinogenesis and other pathologies/diseases is still under investigation. Concern regarding elevated mtDNAcn has been raised by several studies showing an association between an increased mtDNAcn and several cancers, *e.g.* head and neck cancer (Jiang et al., 2005), lung cancer (Hosgood et al., 2010) and breast cancer (Thyagarajan et al., 2013). Besides that, a decrease in mtDNAcn has been associated with Alzheimer's disease (Rice et al., 2014).

While there are no studies reporting mtDNAcn variation for CNT exposure, mtDNAcn variations have been observed for other exposures. A cross-sectional study by Hou et al. Hou et al. (2010) reported higher mtDNAcn, associated with occupational exposure to PM_1, coarse particles ($PM_{2.5\text{-}10}$) and PM_{10}. Another study, conducted by Masayesva et al. Masayesva et al. (2006) has shown an association between cigarette smoking and an increase in mtDNAcn in salivary cells. A study by Tan et al. Tan et al. (2008) supports these results. Moreover, Pavanello et al. Pavanello et al. (2013) reported an increase in mtDNAcn as a result of exposure to polycyclic aromatic hydrocarbons (PAHs). Lee at al. (Lee et al., 2000) has also shown this association between tobacco

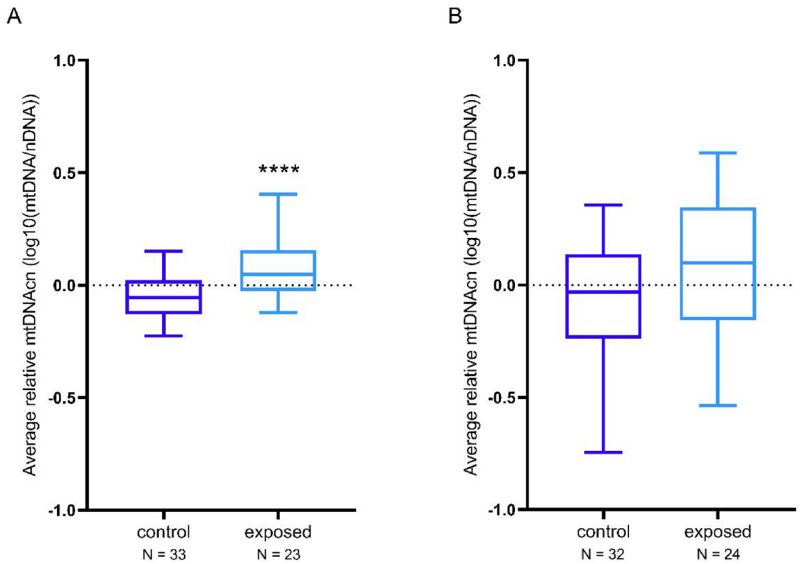

Fig. 1. Box-plots showing the mtDNA content from MWCNT exposed and non-exposed controls, expressed as the log10 of (mtDNA/nDNA) for the two different mitochondrial genes, (A) ND1 and (B) hmito3; ****$p < 0.0001$. P-values based on unpaired *t*-test between exposed and control.

Table 2
Association of mtDNA and TL with CNT exposure.

		mtDNA (ND1)			mtDNA (hmito3)			TL	
	n	% difference (95 %CI)	P-value	n	% difference (95 %CI)	P-value	n	% difference (95 %CI)	P-value
MWCNT exposure									
Non-exposed controls	33	Ref		32	Ref		33	Ref	
MWCNT exposed	23	35.2 (19.1, 53.5)	< 0.0001	24	37.4 (-20.6, 92.8)	0.068	24	18.3 (7.2, 30.6)	0.001
Detailed exposure groups									
Non-exposed controls	33	Ref		32	Ref		33	Ref	
Lab low (1 μg/m^3 EC)	9	26.5 (6.4, 50.7)	0.008	9	23.0 (-22.6, 95.9)	0.38	9	27.1 (10.9, 45.6)	0.001
Lab high (7 μg/m^3 EC)	6	35.5 (10.2, 66.3)	0.004	6	8.9 (-37.2, 88.8)	0.76	6	8.4 (-7.7, 27.4)	0.33
Operator (45 μg/m^3 EC)	6	40.6 (13.8, 73.4)	0.002	7	61.4 (-5.6, 176.7)	0.081	7	18.9 (1.4, 39.0)	0.033

[a]Estimates from the linear regression models provided as a % difference (95 %CI) in outcome compared with the non-exposed group (Ref); MWCNT- Multi-walled carbon nanotube; relative telomere length (TL), mitochondrial copy number (mtDNAcn); ND1 (mitochondrial encoded NADH dehydrogenase 1); Hmito3 (Human mitochondrial genome); Models adjusted for age, sex, smoking behaviour, alcohol consumption and BMI.

smoke and mtDNAcn increase in adjacent lung tissues of patients with cancer. However, several other studies reported contrary findings, *e.g.* a study by Janssen et al. Janssen et al. (2012) reported an inverse association between air pollution exposure and mtDNAcn in placental tissue and Pieters et al. Pieters et al. (2013) reported a decrease in mtDNAcn associated with exposure to PAHs. Mitochondria respond dynamically to environmental insults as reflected by these studies, and depending on the exposure, exposure levels, timing, duration of exposure and study design both positive and negative associations are found. These inconsistencies potentially reflect different phases in the mitochondrial response to environmental exposures, in which both damaging and compensating mechanisms are present. Therefore, alternations in mtDNAcn, may present a biological mechanism by which CNTs, or more specific MWCNTs, affect exposed individuals.

4.2. MWCNT exposure is associated with longer telomere length

The second key finding is that humans exposed to MWCNT have significantly longer telomeres, when compared to non-exposed controls. While this is the first study on TL and CNT exposure, some studies observed longer telomeres in relation to other environmental exposures. Studies have also observed rapid increase in blood TL in response to ambient PM (Dioni et al., 2011; Hou et al., 2012). In addition, some studies report contradictory results. For example, "The Normative Aging Study" found an association between shorter telomeres in and long-term exposures to airborne particles rich in black carbon (Mccracken et al., 2010). A study on the association between arsenic exposure in drinking water and TL showed longer telomeres in peripheral blood after exposure to arsenic acid (Li et al., 2012). They also reported a positive association between urine arsenic levels and telomerase reverse transcriptase gene (TERT) expression.

These findings suggest that carcinogenicity of arsenic among other compounds can be explained by extending the lifespan of possible malignant cells by elongation of the telomeres (Li et al., 2012). A similar observation was made in a Chinese female population, where an association was observed between CLPTM1L-TERT polymorphism, longer TL (measured in peripheral blood) and the risk of lung cancer (Lan et al., 2013). A study by Jones et al. Jones et al. (2012) also found an association between the telomerase RNA component (TERC) polymorphisms and both longer telomeres and susceptibility to colorectal cancer. This suggests that SNPs close to TERC can have functional effects on TERC expression and thus on TL. We acknowledge that only TL was evaluated but other important TL regulating factors, including telomerase activity, epigenetic factors may further explain our findings. In the context of other diseases and carcinogenesis, both positive and negative associations with TL are observed. In a study by Haycock et al.

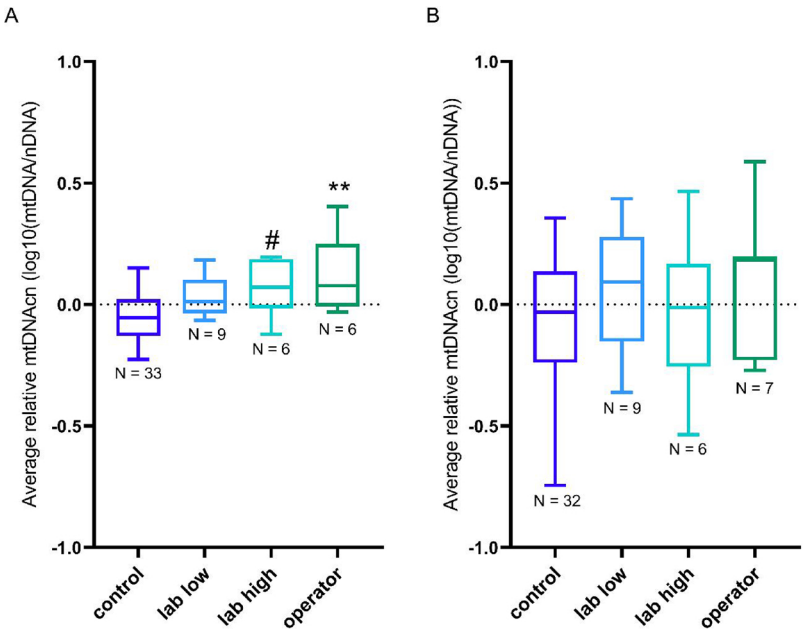

Fig. 2. Box-plots showing the average relative mtDNA content (log10(mtDNA/nDNA)) from both mitochondrial genes, ND1 (A) and Hmito3 (B), for the three different MWCNT exposure groups [lab-low (1 μg/m^3 EC), lab-high (7 μg/m^3 EC), and operators (45 μg/m^3 EC)] compared with the non-exposed controls. # $p < 0.10$, *$p < 0.05$, **$p < 0.01$. P-values based on one-way anova between different exposure groups and the control.

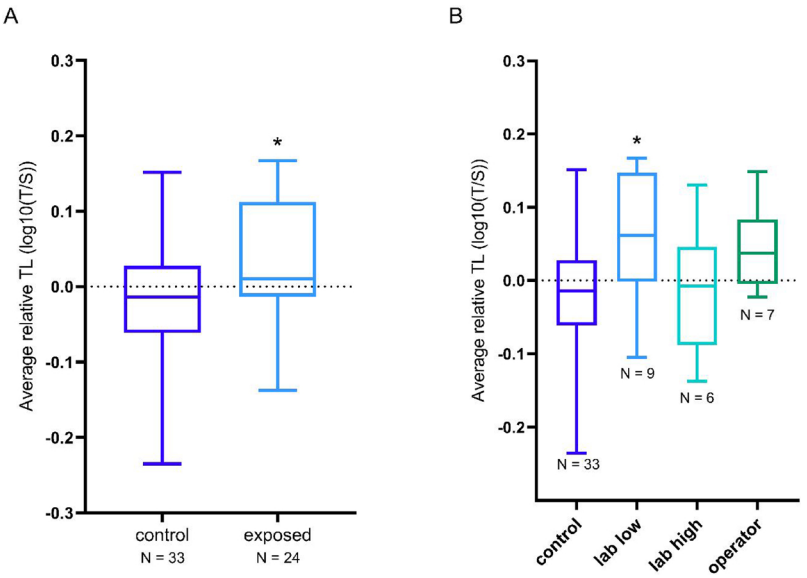

Fig. 3. (A) Box-plot showing the log of the average relative TL of MWCNT exposed workers compared to non-exposed controls (B) Box-plot showing the log of the average TL for the three different groups of exposed workers [lab-low (1 μg/m^3 EC), lab-high (7 μg/m^3 EC), and operators (45 μg/m^3 EC)] compared to non-exposed controls; * $p < 0.05$, ** $p < 0.01$, *** < 0.001. P-values based on unpaired *t*-test (A) and one-way anova (B) between the different exposure groups and control.

Haycock et al. (2017), associations between TL and the risk of cancer and non-neoplastic diseases were studied using a Mendelian randomization study. This study has shown that genetically increased TL is associated with an increased risk of several cancers, *e.g.* melanoma, lung cancer, chronic lymphocytic leukaemia, which has been confirmed by several other prospective observational or Mendelian randomization studies (Zhang et al., 2015; Walsh et al., 2015). It is important to know that these results should be interpreted as a reflection of the average association at the population level. However, these findings are contradictory to those based on retrospective studies, tending to report an association between shorter telomeres and an increased risk for cancer (Ma et al., 2011; Wentzensen et al., 2011). A plausible explanation, proposed by Aviv et al., (Aviv et al., 2017), for the relation between increased TL and cancer, is the potential accumulation of mutation, due to telomere lengthening associated stem-like properties, similar to the findings of Haycock et al. Haycock et al. (2017). Although it is not possible to connect our findings with an increased risk in cancer, it must be said that some studies show an association between long somatic telomeres and some forms of cancer.

We also would like to recognize some strengths and limitations of our study. First, we have a small-sized study and our results need to be confirmed in a larger independent investigation. Nevertheless, we observed robust associations independent of the effect of age, sex, smoking behaviour, alcohol consumption, BMI. We have a well characterized exposure group. Finally, the measurements are conducted only at one time point and therefore a follow-up of the same subject would provide a better interpretation of the present findings.

5. Conclusion

Overall, a higher mtDNAcn and longer telomeres were observed in MWCNT exposed workers when compared to non-exposed controls, independent of age, sex, smoking behavior, alcohol consumption and BMI. When comparing the three groups of exposure (lab low, lab high and operator), significant exposure-associated differences were observed between the groups. While we observe significant change in mtDNAcn and TL in the MWCNT exposed workers, no association can be made regarding possible disease outcome at the moment.

Authors contribution

MG and PH conceptualized the study question and supervised the study. LJ and DSM performed the measurement and analysis (TL and mtDNAcn); TN provided the facility to perform the measurements. LJ, DSM and MG co wrote the manuscript. LG and PH supervised sample collection and processing with other authors (MG; DÖ; JV; AP; EK; RV), which were made available for the present study. All authors facilitated experimentation and provided important feedback during preparation of manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jhazmat.2020.122569.

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