

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Cohort profile. Copenhagen Airport Cohort – air pollution, manual baggage handling and health
<b>AUTHORS</b>	Møller, Karina; Brauer, Charlotte; Mikkelsen, Sigurd; Loft, Steffen; Simonsen, Erik; Koblauch, Henrik; Bern, Stine; Alkjær, Tine; Hertel, Ole; Becker, Thomas; Helweg-Larsen, Karin; Bonde, Jens Peter; Thygesen, Lau

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Luke Knibbs School of Public Health, The University of Queensland, Australia
<b>REVIEW RETURNED</b>	17-Jun-2016

<b>GENERAL COMMENTS</b>	<p>This is a nicely succinct cohort profile paper. The topic at hand is of interest to occupational and environmental health practitioners and researchers given the general lack of studies on airport workers' exposure to air pollutants and manual handling. Hopefully this study will advance the state of knowledge on this topic.</p> <p>However, there are a number of issues I think the authors should address prior to publication. I've outlined these below:</p> <p>P3, Line 40: any details about how many people employed as ground staff globally? This would help set the scene.</p> <p>P3, Line 46: while airports have higher UFP levels, why is this the best exposure metric to assess effects of air pollution? Would a different/additional metric be a better proxy for aviation fuel combustion like VOCs?</p> <p>P5 line 19: following comment above, will this be a study of UFPs or rather the complex mixture that UFPs are a proxy for? I think this should be made clear from the beginning.</p> <p>P5, Line 30: is magnitude the best word here?</p> <p>P5, line 41-49: a schematic diagram showing the layout of the airport, any nearby roads (optional), and where the aprons are would be very useful for the reader.</p> <p>P6, line 44: what are the potential implications of the lack of electronic data from SAS from 1990-95 compared with the longer time span of records from Novia?</p> <p>P7, line 20: some more information on the nature of the unskilled work done by the control group would be good here.</p>
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	<p>P7, line 41: it would be useful if the PPV methods/calculations are presented as a supplement.</p> <p>P9, lines 8-37: did the expert airport personnel have their time assessments validated? Were the times likely to be consistent from 1990-2012 or did the nature of the work change during that time? Were the UFP levels on the apron likely to be similar across 90-12 or did aircraft combustion become more efficient, or conversely were the levels lower in the past because of fewer aircraft movements? These are all questions that should at least be mentioned in the text.</p> <p>P10, lines 34-38: a brief mention of how these models work would be useful for the non-ergonomists.</p> <p>P11, lines 9-28: some of the registers don't fully overlap the cohort (90-12) – please comment on some of the implications of this.</p> <p>P11, line 31: can the effect of things like vapour exposure during refuelling as distinct from combustion emission exposure be separated?</p> <p>P12, line 34: this is an impressive response rate for a postal survey in 2012. Can the authors comment on the reasons for this?</p> <p>P13, line 9-32: the temporal stability of the exposure is relevant here too – is ADT/heavy vehicle share stable over time given it was presumably calculated using present day values? Can the authors comment/demonstrate the validity of these exposure metrics re: their correlation with traffic pollutants (from other studies in the literature perhaps?). Was there any difference in estimated exposure among exact vs non-exact geocodes?</p> <p>P13, Line 36: a section describing analysis methods that will be used seems to be missing here – there's lots of info on exposures and outcomes but nothing on how the data will be analysed. A brief paragraph is needed here.</p> <p>P14 35-51: A brief mention of how this study will extend what is already known about airport workers would help here. Particularly because of the lack of existing information on this topic.</p> <p>P15, lines 25-30: some more discussion of the reference cohort would be useful (see previous comment).</p>
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<b>REVIEWER</b>	Birgit Greiner University College Cork Department of Epidemiology & Public Health Ireland
<b>REVIEW RETURNED</b>	16-Aug-2016

<b>GENERAL COMMENTS</b>	<p>This is a Cohort Profile paper describing the details of the Copenhagen Airport Cohort. Three research studies were already published using the baseline data of this cohort.</p> <p>The study rationale is well written and develops a good argument for</p>
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the establishment of this cohort.

Comments:

Page 4, line 37: The authors state that there is uncertainty regarding the association between occupational exposure to particulate air pollution and health problems with reference to a systematic review. This statement is vague. I suggest to add a brief description about the nature of uncertainty and why this cohort has to offer to overcome this uncertainty.

Page 6, line 10: The cohort comprises men in unskilled jobs. Could a clearer definition be provided, what 'unskilled' jobs are? This would also be relevant in relation to describing the reference cohort. Were both groups truly comparable in this regard?

Page 12, lines 21: what was the stratified random sampling stratified by? Apparently it cannot be stratified by being alive and not alive. How many interviews were done by phone? The response rate of 68.5 is acceptable for this type of study with all kind of logistic problems in reaching workers.

This cohort study involves a range of different methods and level of aggregation of data to assesses and collect exposures, confounders and outcomes, which is a true strength. However it is not easy to follow the methods description. It may be useful to compile a table that briefly summarises the methods for data collection and the main variables broken down by exposures, confounders and health outcomes. This would facilitate the reading of the text and give the reader an instant impression of the main measures used.

I assume that the members of the cohort will be followed up no matter whether they stay in employment with the particular company or as baggage handlers or whether they retire? Maybe the authors could address this issue more clearly.

Page 15, line 25: The authors state that they overcome the healthy worker effect by establishing a reference cohort and hereby diminish this bias. In my view, this statement is not correct. Both groups would be subject to the healthy worker effect as they are occupational cohorts, however by comparing both groups over time one may be able to assess whether there is a differential healthy worker effect in either group.

	<p>Future plans: In my view, the planned scientific contribution of this study in relation to the development of MSDs remains vague. One would like to see a clearer statement about the main types of MSDs that will be investigated and the particular types of associations. It is not particularly novel to investigate whether heavy lifting causes MSDs. Furthermore, MSDs are a tricky outcome to model in cohort studies as they can measure a chronic outcome that lasts for a lifetime, however MSDs can also reverse over time. There appears to be a wealth of data on total baggage lifted per day for the entire sample, biomechanical measurements on a small number and experimental data on handling tasks. How do these come together to investigate specific hypotheses? I understand that a cohort profile paper does not need to include specific details of all planned analyses, however I would expect a brief outline a major lines of hypotheses that could be followed over the next years.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer #1

Reviewer Name: Luke Knibbs

Institution and Country: School of Public Health, The University of Queensland, Australia  
Competing Interests: None declared

This is a nicely succinct cohort profile paper. The topic at hand is of interest to occupational and environmental health practitioners and researchers given the general lack of studies on airport workers' exposure to air pollutants and manual handling. Hopefully this study will advance the state of knowledge on this topic.

However, there are a number of issues I think the authors should address prior to publication. I've outlined these below:

P3, Line 40: any details about how many people employed as ground staff globally? This would help set the scene.

Author response

We agree and have added the following sentence to the text (page 3).

“Globally, more than 2 million civilian and military personnel are occupationally exposed to jet propulsion fuel (1)”.

P3, Line 46: while airports have higher UFP levels, why is this the best exposure metric to assess effects of air pollution? Would a different/additional metric be a better proxy for aviation fuel combustion like VOCs?

Author response

We agree that this could have been stated more precisely in the manuscript and added the following text (page 4-5).

“As a part of a large project to improve the air quality of the working environment, the Danish Centre for Environment and Energy in 2010 estimated air pollution on the apron at Copenhagen Airport. They found that the particle number concentration was two–three times higher on the apron than in a traffic loaded street in the centre of Copenhagen, with 90% of the measured particles in the sizeframe of <100nm (ultrafine particles (UFP))(2). For other pollutants (NO, NO<sub>2</sub>, PM<sub>2.5</sub>, SO<sub>2</sub>, particle mass, concentration of elemental carbon (EC) in the particulate matter, concentration of polycyclic aromatic hydrocarbons (PAH) in the particulate matter and concentration of volatile organic compounds (VOC))

where EU limit values exist all levels measured at Copenhagen Airport were below, but no air quality limit values for particle number exists (3). We therefore assume that if this study found any health effects among airport employees working outdoors, this would be a consequence of exposure to UFP. However, one can only speculate about the degree to which other pollutant may influence any health related effects among airport employees.”

P5 line 19: following comment above, will this be a study of UFPs or rather the complex mixture that UFPs are a proxy for? I think this should be made clear from the beginning.

Author response

We agree that this could have been written more clearly and added the text above (page 4-5).

P5, Line 30: is magnitude the best word here?

Author response

We agree and deleted “magnitude”.

P5, line 41-49: a schematic diagram showing the layout of the airport, any nearby roads (optional), and where the aprons are would be very useful for the reader.

Author response

We have added a map of the airport also showing the apron and the nearby roads page 7 (figure 1).

P6, line 44: what are the potential implications of the lack of electronic data from SAS from 1990-95 compared with the longer time span of records from Novia?

Author response

We added the following text page 20-21.

“We have information on the full employment history of SAS employees from 1995 and onwards. The lack of electronic data from SAS from 1990-1995 means that we have not included employees who stopped their employment before 1995, however, we don’t think this may have introduced bias since we have the whole employment history for those included.”

P7, line 20: some more information on the nature of the unskilled work done by the control group would be good here.

Author response

We agree that this is important information and we have added following to the text (page 10).

”At baseline the majority of the reference group was employed in occupations unexposed to high levels of UFP (e.g. municipal workers, drivers, postal workers, garbage collectors, factory workers)(4). Only few were employed in the construction or welding industry (4%). These groups may have been exposed to high levels of UFP and vehicle exhausts. However, studies of ischemic heart disease in welders indicate that if there is an increased risk, it is small and will hardly contribute to any substantial increased risk in the reference population(5).”

P7, line 41: it would be useful if the PPV methods/calculations are presented as a supplement.

Author response

We agree that this information should be more precise, and furthermore it may be more simple. We have changed the text so that it directly tells the reader how the calculation was made and have omitted the term positive predictive value (PPV) to make the text simpler. After this simplification we think that a supplement is unnecessary to demonstrate PPV calculations.

We changed the succession order of the two paragraphs to emphasize that we prioritized company information over union information.

The text (page 9) now reads as:

“In case of overlapping information, we prioritized data in the company register, because it was mandatory for any salary payment, and we included union information if this supplemented the period before the first entry date of company records. The validity of union information on job function was

assessed by calculating the percentage with the same job function recorded in the company registers. We assessed the validity of questionnaire information on job function the same way. We found good agreement between the data sources. E.g., 87% of persons recorded as baggage handlers by the union were also recorded as baggage handlers in company records, and 92% of persons who in the questionnaire declared that they had worked as security personnel were recorded as such in the company records.

P9, lines 8-37: did the expert airport personnel have their time assessments validated? Were the times likely to be consistent from 1990-2012 or did the nature of the work change during that time? Were the UFP levels on the apron likely to be similar across 90-12 or did aircraft combustion become more efficient, or conversely were the levels lower in the past because of fewer aircraft movements? These are all questions that should at least be mentioned in the text.

Author response

Unfortunately we did not have the resources to validate the time assessed by expert airport personnel. However, this would be a good idea in the future. We have added the following text to the discussion (page 20).

"The number concentration of UFP measured on the apron will probably have changed over time due to a wide range of initiatives from Copenhagen Airport, where diesel powered equipment have been changed with electric equipment. Measurements of UFP was first introduced in 2010, thus the UFP levels of today cannot be compared with levels measured back in time. Working time on the apron near the aircraft could have changed during time, as new and faster equipment are available today. However, with the increasing movements it is not very likely that the actual working time on the apron is different from the past".

P10, lines 34-38: a brief mention of how these models work would be useful for the non-ergonomists.

Author response

We agree and have added the following text (page 13).

"Output from the models was muscle and joint forces. These forces were subsequently used as weights in the register-part of the study."

P11, lines 9-28: some of the registers don't fully overlap the cohort (90-12) – please comment on some of the implications of this.

Author response

"Information from all registers did overlap with the cohort except the prescription register, where data are available since 1995. For this specific register, we may therefore have missed information on outcomes dated before 1995, which could lead to truncation bias".

We have added this to the limitation section on this register (page 20).

P11, line 31: can the effect of things like vapour exposure during refuelling as distinct from combustion emission exposure be separated?

Author response

Unfortunately this is not possibly as outdoor stay is used as a proxy measure for exposure to UFP at the airport. We reworded the text under the exposure section to simplify it (page 12).

P12, line 34: this is an impressive response rate for a postal survey in 2012. Can the authors comment on the reasons for this?

Author response

We think the reason for this relatively high response rate is due to both the method (combination of post mail and telephone) and due to great interest for the project at the airport. During recent years the airport also initiated a wide range of initiatives, e.g. formation of a steering committee and an extended measurement campaign of air pollution at the airport, which also increased focus on this study.

P13, line 9-32: the temporal stability of the exposure is relevant here too – is ADT/heavy vehicle share stable over time given it was presumably calculated using present day values? Can the authors comment/demonstrate the validity of these exposure metrics re: their correlation with traffic pollutants (from other studies in the literature perhaps?). Was there any difference in estimated exposure among exact vs non-exact geocodes?

Author response

The ADT and the heavy-duty share is only provided for the year 2012. In general the heavy-duty share is stable over time as long as looking at the ratio ADT/heavy-duty vehicles, however, the temporal stability of the exposure over time in this case is not known.

Land Use Regression (LUR) has become commonly used tool to estimate exposure in epidemiological studies. In LUR modelling, a simple relationship is statistically derived between traffic densities and various other information and air pollution measurements. The LUR model is then applied to determine exposures at addresses where measurements are not available. In the currently study we are using traffic density and other parameters directly as exposure proxies. Utrecht University in the Netherlands has applied LUR models in the European ESCAPE study and various Dutch cohorts (6) but also previous studies where simple proxies have been applied directly (7). LUR models are usually applied for long-term exposure and cannot resolve inter-annual, weekly and diurnal variations, but they have still proven to be suitable for determining exposure-effect relationships.

Non-exact geo-locations they are placed at the centre of the roads of their residential address, while all correct geo-located points are a bit further away, since the address points representing the house door of the address. For 12,223 men we only had non-exact geocode due to research protection (an option in Danish Law), if they were more or less exposed may be randomly distributed.

P13, Line 36: a section describing analysis methods that will be used seems to be missing here – there's lots of info on exposures and outcomes but nothing on how the data will be analysed. A brief paragraph is needed here.

Author response

We agree and added a section describing analysis methods (page 17-18).

“Analysis methods

For association between air pollution data and health outcomes, we will use survival regression models and include the exposure variable in three different models: 1. the exposed group compared to the reference group. 2. apron-years as a categorical variable (non-exposed, 0.1-2.9 years, 3.0-6.9 years and  $\geq 7$  years), based on the quantile distribution (Q1=0.8, median=2.7 and Q3=6.7). 3. apron-years as a continuous linear variable adjusted for the binary variable (exposed/reference group) to evaluate the influence of cumulative apron-years among the exposed group.

For the influence of manual lifting, we will include a proxy variable of manual lifting as cumulative years of employment as a baggage handler: 1) baggage handlers compared to the reference group. 2. baggage handler cumulative years categorical (reference group, 0.1–2.9 years, 3.0–9.9, 10.0–19.9 and 3. cumulative years as a continuous variable.

For both analyses we will also investigate the non-linear influence of the exposure variables using restricted cubic spline regression.”

P14 35-51: A brief mention of how this study will extend what is already known about airport workers would help here. Particularly because of the lack of existing information on this topic.

Author response

We have added the following text under the section strengths and limitations (page 19-20).

“Finally, this cohort will contribute with long-term follow-up information on health and airport work, which is lacking at present.”

P15, lines 25-30: some more discussion of the reference cohort would be useful (see previous

comment).

Author response

We agree and added this in the text - see previous comment.

Reviewer #2

Reviewer Name: Birgit Greiner

Institution and Country: University College Cork, Department of Epidemiology & Public Health, Ireland

Competing Interests: None declared

This is a Cohort Profile paper describing the details of the Copenhagen Airport Cohort. Three research studies were already published using the baseline data of this cohort.

The study rationale is well written and develops a good argument for the establishment of this cohort.

Page 4, line 37: The authors state that there is uncertainty regarding the association between occupational exposure to particulate air pollution and health problems with reference to a systematic review. This statement is vague. I suggest to add a brief description about the nature of uncertainty and why this cohort has to offer to overcome this uncertainty.

Author response

We have added a short description to the text (page 5).

“Over the past 10 years, the scientific interest has moved from mass concentration (PM2.5 and PM10) to the number concentration of UFP (8). UFP differs from larger particles due to the large surface area with adhered toxins and high alveolar deposition (9). Several experimental studies in animals have shown that UFP can translocate into the blood vessels due to the small size (9-13), and this is likely to occur in humans although translocation from the lungs has not been firmly established (14).

Ground personnel working on the apron near and around the aircraft are exposed to exhaust from jet fuel and diesel exhaust from handling equipment (2). Previous studies have shown that the major sources of UFP are emissions from motor vehicles and other combustion machines (9, 15).”

Page 6, line 10: The cohort comprises men in unskilled jobs. Could a clearer definition be provided, what ‘unskilled’ jobs are? This would also be relevant in relation to describing the reference cohort. Were both groups truly comparable in this regard?

Author response

In this cohort we included men in unskilled work. The main part of the reference group included men employed in mail service, stockroom and security, however approximately 4% of the group consisted at baseline of men employed in the construction or welding industry. A sentence about this is added to the text (page 10).

Page 12, lines 21: what was the stratified random sampling stratified by? Apparently it cannot be stratified by being alive and not alive. How many interviews were done by phone? The response rate of 68.5 is acceptable for this type of study with all kind of logistic problems in reaching workers.

Author response

The stratified random sampling was stratified by sub-union or company. The questionnaires were delivered to all baggage handlers and all currently employed security service personnel in Copenhagen Airport during April 2012. For the remaining groups (CPH-company, NUGSP, 3F Kastrup with other jobs at the airport, 3F Kastrup without work at the airport, and the two other 3F unions (LPSF and 3F Mølleåen)) and for previously employed security service personnel, we used stratified random sampling.

Out of 5,474 men a total of 3,749 responded to the questionnaire. 433 were obtained from telephone interview.

Following was added to the text (page 15).

“...( CPH-company, NUGSP, 3F Kastrup with other jobs at the airport, 3F Kastrup without work at the



airport, and the two other 3F unions (LPSF and 3F Mølleåen) and for previously employed security service personnel)“...

“...433 were obtained from telephone interview...”

This cohort study involves a range of different methods and level of aggregation of data to assesses and collect exposures, confounders and outcomes, which is a true strength. However it is not easy to follow the methods description. It may be useful to compile a table that briefly summarises the methods for data collection and the main variables broken down by exposures, confounders and health outcomes. This would facilitate the reading of the text and give the reader an instant impression of the main measures used.

Author response

We think this is a good idea. A table illustrating data and collection is added to the manuscript (page 12 table 2).

I assume that the members of the cohort will be followed up no matter whether they stay in employment with the particular company or as baggage handlers or whether they retire? Maybe the authors could address this issue more clearly.

Author response

This is correct and we agree that this information can be useful in understanding data for analysis. We added the below section (page 17).

“Analyses

The cohort will be followed from start of employment, 1st January 1990 or immigration after employment, whichever came last, and until first diagnosis of outcome under study, emigration, death or end of follow-up (31 December 2012), whichever came first. This means that cohort members also will be followed after possible end of employment. We will exclude persons with a diagnosis of outcome under study before 1990 and persons who only had employment after a diagnosis of outcome under study. ”

Page 15, line 25: The authors state that they overcome the healthy worker effect by establishing a reference cohort and hereby diminish this bias. In my view, this statement is not correct. Both groups would be subject to the healthy worker effect as they are occupational cohorts, however by comparing both groups over time one may be able to assess whether there is a differential healthy worker effect in either group.

Author response

We agree with the reviewer. The word “overcome” is misleading. We have rephrased the sentence page 21:

“To diminish this potential bias, we established a reference cohort consisting of men in unskilled jobs other than in airports (16, 17)”

Future plans: In my view, the planned scientific contribution of this study in relation to the development of MSDs remains vague. One would like to see a clearer statement about the main types of MSDs that will be investigated and the particular types of associations. It is not particularly novel to investigate whether heavy lifting causes MSDs. Furthermore, MSDs are a tricky outcome to model in cohort studies as they can measure a chronic outcome that lasts for a lifetime, however MSDs can also reverse over time. There appears to be a wealth of data on total baggage lifted per day for the entire sample, biomechanical measurements on a small number and experimental data on handling tasks. How do these come together to investigate specific hypotheses? I understand that a cohort profile paper does not need to include specific details of all planned analyses, however I would expect a brief outline a major lines of hypotheses that could be followed over the next years.

Author response

We have added the following text page 21.

“We intend to explore correlations between specific morbidity by e.g. ischemic heart diseases, stroke,

lung and bladder cancer, asthma and chronic obstructive pulmonary disease and occupational exposures at airports. In addition we plan to assess dose-response relationships between heavy lifting, stooped postures and kneeling and musculoskeletal disorders in the low back, shoulders and knees by combining data from the biomechanical measurements with data on handled baggage per day and employment history. Furthermore we will have focus on studies on work status and prognostic studies in relation to the musculoskeletal disorders.”

## References

1. Ritchie G, Still K, Rossi J, 3rd, Bekkedal M, Bobb A, Arfsten D. Biological and health effects of exposure to kerosene-based jet fuels and performance additives. *Journal of toxicology and environmental health Part B, Critical reviews*. 2003;6(4):357-451.
2. Ellermann T, Massling A, Løfstrøm P, Winther M, Nøjgaard J, Ketzel M. Assessment of the air quality at the apron of Copenhagen Airport Kastrup in relation to the working environment. 2012.
3. Committee AEES. Ultrafine Particles at Airports. Discussion and assessment of ultrafine particles (UFP) in aviation and at airports in 2012.
4. Mikkelsen S, Brauer C, Pedersen EB, Alkjaer T, Koblauch H, Simonsen EB, et al. A Cohort Study on Meniscal Lesions among Airport Baggage Handlers. *PloS one*. 2016;11(6):e0157336.
5. Sjogren B, Fossum T, Lindh T, Weiner J. Welding and ischemic heart disease. *International journal of occupational and environmental health*. 2002;8(4):309-11.
6. de Hoogh K, Korek M, Vienneau D, Keuken M, Kukkonen J, Nieuwenhuijsen MJ, et al. Comparing land use regression and dispersion modelling to assess residential exposure to ambient air pollution for epidemiological studies. *Environment international*. 2014;73:382-92.
7. Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. *Lancet (London, England)*. 2002;360(9341):1203-9.
8. Franck U, Odeh S, Wiedensohler A, Wehner B, Herbarth O. The effect of particle size on cardiovascular disorders--the smaller the worse. *The Science of the total environment*. 2011;409(20):4217-21.
9. Delfino RJ, Sioutas C, Malik S. Potential role of ultrafine particles in associations between airborne particle mass and cardiovascular health. *Environmental health perspectives*. 2005;113(8):934-46.
10. Li N, Sioutas C, Cho A, Schmitz D, Misra C, Sempf J, et al. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. *Environmental health perspectives*. 2003;111(4):455-60.
11. Nemmar A, Hoet PH, Vanquickenborne B, Dinsdale D, Thomeer M, Hoylaerts MF, et al. Passage of inhaled particles into the blood circulation in humans. *Circulation*. 2002;105(4):411-4.
12. Donaldson K, Stone V, Seaton A, MacNee W. Ambient particle inhalation and the cardiovascular system: potential mechanisms. *Environmental health perspectives*. 2001;109 Suppl 4:523-7.
13. Oberdorster G, Finkelstein J, Ferin J, Godleski J, Chang LY, Gelein R, et al. Ultrafine particles as a potential environmental health hazard. Studies with model particles. *Chest*. 1996;109(3 Suppl):68s-9s.
14. Rinaldo M, Andujar P, Lacourt A, Martinon L, Canal Raffin M, Dumortier P, et al. Perspectives in Biological Monitoring of Inhaled Nanosized Particles. *The Annals of occupational hygiene*. 2015;59(6):669-80.
15. Dominguez-Rodriguez A, Abreu-Afonso J, Rodriguez S, Juarez-Prera RA, Arroyo-Ucar E, Jimenez-Sosa A, et al. Comparative study of ambient air particles in patients hospitalized for heart failure and acute coronary syndrome. *Revista espanola de cardiologia*. 2011;64(8):661-6.
16. Thygesen LC, Hvidtfeldt UA, Mikkelsen S, Bronnum-Hansen H. Quantification of the healthy worker effect: a nationwide cohort study among electricians in Denmark. *BMC public health*. 2011;11:571.
17. Steenland K, Stayner L. The importance of employment status in occupational cohort mortality studies. *Epidemiology (Cambridge, Mass)*. 1991;2(6):418-23.

<b>REVIEWER</b>	Luke Knibbs School of Public Health, The University of Queensland, Australia.
<b>REVIEW RETURNED</b>	21-Oct-2016

<b>GENERAL COMMENTS</b>	<p>The authors have made a reasonable attempt at responding to most of my previous comments. There are two responses that require further clarification noted below. Assuming these are addressed adequately, then I think the paper is ready for acceptance.</p> <p>Pages 4-5      “As a part of a large project to improve the air quality of the working environment, the Danish Centre for Environment and Energy in 2010 estimated air pollution on the apron at Copenhagen Airport. They found that the particle number concentration was two–three times higher on the apron than in a traffic loaded street in the centre of Copenhagen, with 90% of the measured particles in the sizeframe of &lt;100nm (ultrafine particles (UFP))(2). For other pollutants (NO, NO2, PM2.5, SO2, particle mass, concentration of elemental carbon (EC) in the particulate matter, concentration of polycyclic aromatic hydrocarbons (PAH) in the particulate matter and concentration of volatile organic compounds (VOC)) where EU limit values exist all levels measured at Copenhagen Airport were below, but no air quality limit values for particle number exists (3). We therefore assume that if this study found any health effects among airport employees working outdoors, this would be a consequence of exposure to UFP. However, one can only speculate about the degree to which other pollutant may influence any health related effects among airport employees.”</p> <p>I think this new text is an improvement, but the assumption of observed health effects being due to UFP because the other pollutants are below EU limits is a dangerous and potentially misleading one. The last two sentences of this paragraph should be deleted so that they don’t undermine the rest of the paper.</p> <p>Page 7.      ”At baseline the majority of the reference group was employed in occupations unexposed to high levels of UFP (e.g. municipal workers, drivers, postal workers, garbage collectors, factory workers)(4). Only few were employed in the construction or welding industry (4%). These groups may have been exposed to high levels of UFP and vehicle exhausts. However, studies of ischemic heart disease in welders indicate that if there is an increased risk, it is small and will hardly contribute to any substantial increased risk in the reference population(5).”</p> <p>The authors have elaborated on the characteristics of the reference groups, which is good. However, the text needs clarification – are they saying that these groups are or aren’t more exposed than airport workers? If they saying that those groups are relatively unexposed, then I disagree because garbage collectors (lots of proximity to stop-start diesel trucks) and drivers (lots of proximity to tailpipe emissions), and potentially some of the other occupations in the reference group, are exposed to high levels of UFP. This needs to be defended more rigorously (e.g. if the authors have evidence to back up the assertion that these groups are less exposed). If not, the inclusion of these occupations in the reference group should be strongly reconsidered and this noted in the text.</p>
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## VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Luke Knibbs

Institution and Country: School of Public Health, The University of Queensland, Australia.

Competing Interests: None declared.

The authors have made a reasonable attempt at responding to most of my previous comments. There are two responses that require further clarification noted below. Assuming these are addressed adequately, then I think the paper is ready for acceptance.

Pages 4-5

“As a part of a large project to improve the air quality of the working environment, the Danish Centre for Environment and Energy in 2010 estimated air pollution on the apron at Copenhagen Airport. They found that the particle number concentration was two–three times higher on the apron than in a traffic loaded street in the centre of Copenhagen, with 90% of the measured particles in the sizeframe of <100nm (ultrafine particles (UFP))(2). For other pollutants (NO, NO<sub>2</sub>, PM<sub>2.5</sub>, SO<sub>2</sub>, particle mass, concentration of elemental carbon (EC) in the particulate matter, concentration of polycyclic aromatic hydrocarbons (PAH) in the particulate matter and concentration of volatile organic compounds (VOC)) where EU limit values exist all levels measured at Copenhagen Airport were below, but no air quality limit values for particle number exists (3). We therefore assume that if this study found any health effects among airport employees working outdoors, this would be a consequence of exposure to UFP. However, one can only speculate about the degree to which other pollutant may influence any health related effects among airport employees.”

I think this new text is an improvement, but the assumption of observed health effects being due to UFP because the other pollutants are below EU limits is a dangerous and potentially misleading one. The last two sentences of this paragraph should be deleted so that they don't undermine the rest of the paper.

Author response

We agree and deleted the two last sentences.

Reviewer comments

Page 7.

“At baseline the majority of the reference group was employed in occupations unexposed to high levels of UFP (e.g. municipal workers, drivers, postal workers, garbage collectors, factory workers)(4). Only few were employed in the construction or welding industry (4%). These groups may have been exposed to high levels of UFP and vehicle exhausts. However, studies of ischemic heart disease in welders indicate that if there is an increased risk, it is small and will hardly contribute to any substantial increased risk in the reference population(5).”

Author response

At baseline the reference group worked in a variety of different occupations (e.g. municipal workers, drivers, postal workers, garbage collectors, factory workers etc)(1). We do not have representative measures of UFP and vehicle exhaust for the various occupations. However, we are convinced that only few occupations and few persons in the reference group were continuously exposed to UFP or vehicle exhaust at a similar level as on the apron at Copenhagen Airport. Temporary high exposure levels may occur among drivers, garbage collectors, and in the welding and construction industries. However, in the absence of specific exposure information and considering that such groups with potentially high exposures were relatively few, we decided to not to exclude any specific occupations from the reference group. The effect may be a slightly diluted difference in exposure related effects between the reference group and the exposed group.

Reviewer comments

The authors have elaborated on the characteristics of the reference groups, which is good. However,

the text needs clarification – are they saying that these groups are or aren't more exposed than airport workers? If they saying that those groups are relatively unexposed, then I disagree because garbage collectors (lots of proximity to stop-start diesel trucks) and drivers (lots of proximity to tailpipe emissions), and potentially some of the other occupations in the reference group, are exposed to high levels of UFP. This needs to be defended more rigorously (e.g. if the authors have evidence to back up the assertion that these groups are less exposed). If not, the inclusion of these occupations in the reference group should be strongly reconsidered and this noted in the text.

**Author response**

Thank you for this challenging and important statement.

There was a mistake in the manuscript connecting the examples of occupations with low exposure. These aspects should have been considered separately. We agree with you that some occupations or persons may have high exposures. However we have no direct measurements on occupational exposures in the reference group.

We do not completely agree with your examples of high exposures, although we cannot exclude that you are right. The UFP concentration in Copenhagen Airport was approximately three times as high as on the Copenhagen street (H.C. Andersens Boulevard) with heaviest traffic during rush hours, leaving some room, perhaps, to a lower exposure among drivers than in Copenhagen airport.

In our opinion, most garbage collectors in Denmark have fairly little exposure to stop-start diesel exhaust because diesel exhaust is ventilated above the vehicle at the front, the diesel engine is usually stopped during stand still and the garbage emptying system is worked by hydraulic electrical equipment at the rear. When the diesel engine is started again, the garbage collectors are on their way to collect new garbage at a distance from the vehicle. However, this is all points of view, and may prove wrong, if data could be established.

We have changed the text page 9 to reflect these considerations without going into detail and hope that it will address your concerns:

“At baseline the reference group worked in a variety of different occupations (e.g. municipal workers, drivers, postal workers, garbage collectors, factory workers etc) (1). We do not have representative measures of UFP and vehicle exhaust for the various occupations. However, we are convinced that only few occupations and few persons in the reference group were continuously exposed to UFP or vehicle exhaust at a similar level as on the apron at Copenhagen Airport. Temporarily high exposure levels may occur among drivers, garbage collectors, and in the welding and construction industries. However, in the absence of specific exposure information and considering that such groups with potentially high exposures were relatively few, we decided to not to exclude any specific occupations from the reference group. The effect may be a slightly diluted difference in exposure related effects between the reference group and the exposed group.”

**VERSION 3 – REVIEW**

<b>REVIEWER</b>	Luke Knibbs University of Queensland, School of Public Health, Australia.
<b>REVIEW RETURNED</b>	19-Jan-2017

<b>GENERAL COMMENTS</b>	The response to my previous comments is adequate and I recommend acceptance.
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