OCCUPATIONAL NOISE EXPOSURE AND RISK FOR CARDIOVASCULAR DEATHS AND ACUTE MYOCARDIAL INFARCTION

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Noise is said to be as one of the most intense and hazardous environmental and occupational exposures causing auditory as well as non-auditory health problems. The cardiovascular related health problems are very common in occupational setting. Hence, the effect of occupational noise exposure on health and its risk for cardiovascular disease (CVD) and deaths cannot be neglected.

The aim of this study was to explore the association between occupational noise exposure and risk for Coronary Heart Disease (CHD) deaths, stroke deaths and Acute Myocardial Infarction (AMI) where noise exposure group and noise-years were used as exposures to measure the association.

The study comprised male participants from baseline cohorts of Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) who belonged to different occupational groups. Altogether, 2130 participants were included in the study based on the availability of data. The participants completed three sets of questionnaires and went through clinical examinations in the study center. The outcomes; CHD deaths and stroke deaths were measured from National Death Registry by using Finnish personal identification codes. For the AMI, the data was extracted from the record linkage with national hospitalization discharge registries. Descriptive analyses were used in the study to find out the distribution of variables in noise exposure group (unexposed and exposed). Correlation analysis and binary logistic regressions were used for finding the confounders. Cox Regression analysis was performed to calculate hazard ratio at 95% Confidence Interval (CI) between noise exposure group and noise-years separately with the outcomes; CHD deaths, stroke deaths and AMI where the confounders were adjusted.

The results of this study were consistent with no associations between exposures; noise exposure group and noise-years with the outcomes CHD deaths, stroke deaths and AMI. Lack of literatures on occupational noise and CVD outcomes and CVD deaths makes it important to study the association and draw reliable conclusions. Hence, this study helps in fulfilling the gap in knowledge and further explore the results for the association between occupational noise with CHD deaths, stroke deaths and AMI.
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Thank you.

Kuopio, September 2017
Sujala Mathema
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<tr>
<th>Abbreviation</th>
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<tr>
<td>AMI</td>
<td>Acute Myocardial Infarction</td>
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<td>ANS</td>
<td>Autonomic Nervous System</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<td>BP</td>
<td>Blood Pressure</td>
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<td>CDC</td>
<td>Central for Disease Control</td>
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<td>CHD</td>
<td>Coronary Heart Disease</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>CORDIS</td>
<td>Cardiovascular Occupational Risk Factor Determination</td>
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<td>CVD</td>
<td>Cardiovascular Disease</td>
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<td>DALYs</td>
<td>Disability-Adjusted Life Years</td>
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<td>dB</td>
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<td>DBP</td>
<td>Diastolic Blood Pressure</td>
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<td>ED</td>
<td>Endothelial Dysfunction</td>
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<td>EDRF</td>
<td>Endothelium-Derived Relaxing Factor</td>
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<td>FINMONICA</td>
<td>Finnish Monitoring of Trends and Determinants of Cardiovascular Diseases</td>
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<td>HDL</td>
<td>High-Density Lipoprotein</td>
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<td>HPA</td>
<td>Hypothalamic Pituitary Adrenocortical</td>
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<td>HR</td>
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<td>HRT</td>
<td>Hormone Replacement Therapy</td>
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<td>HRV</td>
<td>Heart Rate Variability</td>
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<td>ICD</td>
<td>International Classification of Diseases</td>
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<td>IHD</td>
<td>Ischemic Heart Disease</td>
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<td>IL-6</td>
<td>Interleukin-6</td>
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<td>JEM</td>
<td>Job-Exposure Matrix</td>
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<td>KIHD</td>
<td>Kuopio Ischemic Heart Disease Risk Factor Study</td>
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<td>LDL</td>
<td>Low-Density Lipoprotein</td>
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<td>LVH</td>
<td>Left Ventricular Hypertrophy</td>
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<td>MI</td>
<td>Myocardial Infarction</td>
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<td>Acronym</td>
<td>Definition</td>
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<td>MONICA</td>
<td>Monitoring of Trends and Determinants of Cardiovascular Diseases</td>
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<td>NaRoMI</td>
<td>Noise and Risk of Myocardial Infarction</td>
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<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
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<td>NHIS</td>
<td>National Health Interview Survey</td>
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<td>NO</td>
<td>Nitric Oxide</td>
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<td>PAR</td>
<td>Population Attributable Risk</td>
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<td>PM</td>
<td>Particulate Matter</td>
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<td>PNS</td>
<td>Parasympathetic Nervous System</td>
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<td>QoL</td>
<td>Quality of Life</td>
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<td>SAM</td>
<td>Sympathetic Adrenal Medullar</td>
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<td>SBP</td>
<td>Systolic Blood Pressure</td>
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<td>SBU</td>
<td>Swedish Agency for Health Technology Assessment and Assessment of Social Services</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>SNS</td>
<td>Sympathetic Nervous System</td>
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<td>STEMI</td>
<td>ST-elevation MI</td>
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<td>US</td>
<td>United States</td>
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1. INTRODUCTION

Noise is said to be as one of the most intense and hazardous environmental and occupational exposures (Davies et al. 2005, Willich et al. 2006). The health burden due to environmental noise was quantified in disability-adjusted life years (DALYs; number of years lost due to disability or death, a combined measurement of morbidity and mortality) by World Health Organization (WHO) report in 2011. Annually, cognitive impairment caused by noise is responsible for 45000 years of life lost in children, disturbance in sleep due to noise cause 903000 years of life lost, cardiovascular disease (CVD) due to noise cause 61000 years of life lost and 22000 years of life lost due to tinnitus. Likewise, noise annoyance reduces the quality of life (QoL) leading to disability and cause 587000 DALYs in the population of Western Europe (WHO 2011, Münzel et al. 2014).

The data for occupational noise is very scarce in developing countries. The average occupational noise levels in developing countries were higher than the recommended noise levels in many developed countries (Suter 2003). A survey conducted on workers in the European Union, indicated that one-fourth of the time, 28% of workers were exposed to a loud occupational noise level of approximately 85-90 decibels (dB) where the workers had to raise their voice to have a normal conversation (Nelson et al. 2005). Likewise, in the United States (US), around 22.4 million (17.2%) workers were found to be exposed to noise level considered as hazardous at the workplace (Tak et al. 2009).

Annually, CVD is responsible for higher number of deaths than other diseases and more than three-quarters of deaths due to CVD occurs in low and middle-income countries (WHO 2017a). Globally, four out of five deaths are contributed by heart attacks and strokes (WHO 2017b). In Finland, CVD is the second major cause of death among working age group (OSF 2014). In the US, every year, one in three deaths is contributed by CVD where Coronary Heart Disease (CHD) and stroke is responsible for most of those deaths. Based on the data of National Health Interview Survey (NHIS), Central for Disease Control (CDC), the workers who were involved in services and blue-collar workers reported a history of CHD or stroke more often compared to white-collar workers (Luckhaupt & Calvert 2014). Likewise, significant increase in risk for acute myocardial infarction (AMI) was found across different occupations and industries in the US (Robinson et al. 2015).
As mentioned by Skogstad et al. (2016), noise is found to be associated with many health problems and suggested that based on previous scientific research, noise might possibly lead to CVD. Davies et al. (2005) taking reference to much older studies (Folkow 1989, Bjorntorp 1997), explained that noise is thought to cause CVD due to the repeated stress response which makes the sympathetic and neuroendocrine system pathogenic leading to hypertension and over secretion of cortisol causing fat accumulation.

There are many studies on CVD and environmental noise but very few on CVD and occupational noise. Among those few studies on occupational noise and CVD, relatively less studies focused on the association between occupational noise exposure with CVD deaths. The association between CHD deaths, stroke deaths and AMI from the previous studies were found to be inconsistent. Thus, to investigate the inconsistent associations from previous findings, this study aims to further explore the association between occupational noise exposure and risk for CHD deaths, stroke deaths and AMI.
2. LITERATURE REVIEW

2.1 Noise
There is no unanimous definition on noise, however, in a report by WHO (Barrientos et al. 2004), noise is considered as unwanted or undesired sound. The report explains that noise is present in all activities done by the human and is differentiated as occupational or environmental noise. Occupational noise is the noise in the occupational settings and environmental noise includes noise at every other setting at community or residential or domestic levels. The occupational noise regulatory limit is usually 85 dB(A) in developed and 90 dB(A) in developing countries for an 8-hour day. In addition, the minimum noise exposure in work setting is considered as noise exposure less than 85 dB(A), moderate high noise exposure as 85–90 dB(A) and high noise exposure greater than 90 dB(A) (Barrientos et al. 2004).

2.1.1 Noise as a stressor
As mentioned by Recio et al. (2016), in a stress model illustrated by McEwen (1998), noise is considered as a psychological stressor and can disrupt homeostasis. An individual becomes stable when one adapts to challenges of changing environment through allostasis to achieve homeostasis. The changes in allostatic load can affect stress response. Aich et al. (2009) explained that in mammals, the allostasis is regulated by hypothalamic pituitary adrenocortical (HPA) axis. HPA in mammals works in correspondence with the sympathetic adrenal medullar (SAM) axis. HPA enhances glucocorticoid secretions like cortisol with elongated response to defensive physiology and SAM has a immediate reaction to acute stress with catecholamine secretion.

There are basically two ways of coping with acute stress as mentioned by Lundberg (1999). The first strategy is the active strategy where “fight or flight” response takes place to control or overcome stress by activating SAM with catecholamine secretion. The second is the repressed strategy where there is feeling that stress could not be controlled that produce “defeat” response and activates HPA with cortisol release. Recio et al. (2016) explained that in situations like road traffic noise where noise is not possible to control, there is defeat response resulting to HPA activation and cortisol release. The study also illustrates about effects of cortisol overproduction (Sapolsky et al. 1986) and reveals that cortisol overproduction can damage the hippocampus which affects the brain in its memory functioning and reception of cortisol and produce cortisol irrespective of the presence of stress. Stress also depends on sensitivity as at what extend a person
is sensitive. The interaction between certain noise level with sensitivity can trigger some extend to annoyace and annoyance can be a part of the mechanism of noise to produce some health events (Ndrepepa & Twardella 2011). It was reported in Stosić et al. (2009) that being too sensitive to traffic noise could increase the risk of cortical arousal.

2.1.2 Measurement of noise levels

The noise levels are measured in subjective as well as objective or quantitative ways. Usually, noise levels are measured in quantitative manner using noise exposure meter or dosimeter readings. According to a report by WHO (Barrientos et al. 2004), the measurement of noise levels depends on physical quantities that are based on noise frequency, noise characteristics like impulse and continuous or intermittent noise levels and source of noise to refer for the sensitivity of noise to the people. Impulse noise is usually defined as noise with single bursts having less than one second of duration and with peak levels more than 15 dB compared to background noise. The difference between impulse and steady noise depends on noise duration (Starck et al. 2003). According to Canadian Union of Public Employees (2006), constant noise is considered as continuous noise and intermittent noise is a combination of quiet and noise period. The report of WHO (Barrientos et al. 2004) gave three distinct ways to measure noise levels at workplace;

a. Sound pressure level: The air vibration which make sound is measured by sound pressure level (L) and is measured in dB to refer the loudness produced by sound.

b. Sound level: Human ear perceives sounds at different frequencies, thus to weight level of sound pressure at different frequencies, a spectral sensitivity factor is applied which is indicated as A-filter and is expressed in dB(A).

c. Equivalent sound levels: The sound levels differ in time; thus, equivalent sound level is considered over the specific period. The A-weighted sound level is taken over specific time period (T) and is indicated as $L_{A_{eq,T}}$.

In contrast, subjective noise is usually measured using a set of questionnaires. In a noise level assessment research by Beach et al. (2011), the study used ten-point Likert scale from 1 to 10 with questions ranging from “very quiet” to “very loud”. The study participants had to fill up a diary record comprising daily routine of activities and events. The results of the assessment indicated that individuals could successfully estimate noise levels they experience in their daily events. Likewise, a study by Willich et al. (2006), used five-point Likert scale to measure noise annoyance
in a scale of 1 to 5 comprising questions from “not annoyed at all” to “extremely annoyed” both in environmental and workplace noise to measure noise burden with the risk of myocardial infarction (MI). Furthermore, a study by Schlaefer et al. (2009) reported that the subjective or self-reported noise exposure in occupational setting is considered as a valid exposure metric. In addition, the study explained that noise exposure is appropriate when noise exposure information is available for longest job. Nevertheless, Ahmed et al. (2004) used simple questions in his study to measure the self-reported noise levels at occupational settings.

2.2 Cardiovascular disease (CVD)
According to WHO (2017b), “Cardiovascular diseases are disorders of the heart and blood vessels and include coronary heart disease, cerebrovascular disease, rheumatic heart disease and other conditions”.

2.2.1 Risk factors for CVD
The risk factors for CVD can be classified into modifiable and non-modifiable risk factors. The World Heart Federation (2017) has further explained the classification as follows:

Modifiable risk factors:

Hypertension is one of the prominent risk factors for CVD causing stroke or heart attacks and can be prevented if diagnosed on time and follow management plan as instructed. Likewise, the risk for CVD increases with increase in abnormal levels of blood lipid levels like high total cholesterol levels, high triglyceride levels, high low-density lipoprotein (LDL) levels or low high-density lipoprotein (HDL) cholesterol levels. Adaptation of healthy lifestyle with medications can reduce the abnormalities and improve blood lipid profile. Use of tobacco either smoking or by chewing increases risk for CVD. Passive smoking can be equally harmful as direct smoking and the effects are modifiable if the use of tobacco is stopped as soon as possible.

Almost half of the CVD risk is contributed by physical inactivity where obesity plays the key role as a risk factor for CVD and increases the chance of development of Type 2 diabetes. In addition, a person with diabetes is twice more likely to develop CVD compared to those who does not have diabetes. Thus, if an immediate measure to control diabetes is not carried out, can result in the earlier development of CVD and the situation is even worse in pre-menopausal women where the estrogen hormonal effect is destroyed by diabetes resulting to increased risk for CVD. High
saturated fat content diet increases the risk for CVD and globally it is estimated to cause approximately 31% of CHD and 11% stroke. Poverty invites stressful life events like social isolation causing anxiety, depression increasing the risk for CVD. An elevated level of alcohol intake is also considered as risk factor for CVD. On the contrary, consumption of one to two alcohol per day assumed to reduce heart disease by 30%. Medications like contraceptive pills and hormone replacement therapy (HRT) are also responsible for increased risk for heart disease. Lastly, left ventricular hypertrophy (LVH) is also considered as risk factor for CVD mortality.

Non-modifiable risk factors:

Aging is another risk factor for CVD where after 55 years of age, the risk for stroke gets double every decade. Family history also determines the risk for CVD. The risk for CVD increases if blood-related family members like parents had a history of CVD. There is no difference in risk of heart disease between male and female but in the case of pre-menopausal women, the risk of heart disease is significantly lower compared to male. However, the risk for stroke is similar in both sexes. Ethnic background is a major contributor for CVD as people of Africa and Asia are at increased risk for development of CVD.

2.2.2 CVD outcomes

The American Heart Association (2017a) has explained CVD outcomes as follows:

Coronary Heart Disease: CHD is a very common type of heart disease and is also termed as coronary artery disease. CHD develops when plaque buildup in the arteries of the heart which is called atherosclerosis. The arteries narrow down making blood flow difficult due to plaques and this reduction of blood flow to the heart may lead to angina commonly known as chest pain or even heart attack and in long term can result in heart failure and arrhythmias.

Stroke: An interruption of blood flow to the brain resulting in paralysis, slurred speech, and change in brain function is known as stroke. Ischemic stroke occurs due to the blockage of blood vessel carrying blood to the brain and around nine of every 10 strokes are caused by ischemic stroke. Hemorrhagic stroke occurs due to the bursting of blood vessels. The symptoms include immediate insensibility or weakness of the face, arm or leg; disorientation with the problem in verbal communication or understanding, vision impairment; difficulty in walking due to dizziness or imbalance or poor coordination and severe headache with the unknown cause.
Myocardial infarction: MI is referred as the heart attack in medical terms. The blockage of blood supply to an area in the heart muscle causes damage or death to that area. Another specific term used for heart attack is the ST-elevation MI, also referred as STEMI. If there is blockage of blood supply for a longer period it affects a huge portion of the heart and increases the risk of death and disability.

2.3 Noise and CVD

2.3.1 Effects of noise on health
Exposure to noise is very common in occupational settings and is known to cause health hazard in the world with considerable effects in social and physiological conditions. The most prominent health effect due to noise is the hearing loss (Suadicani et al. 2012).

Globally, CVD is considered as the number one cause of mortality (WHO 2017a). As mentioned by Passchier and Passchier (2000), there are many research that shows noise causing auditory as well as non-auditory health effects including ischemic heart disease (IHD). According to Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU 2015), both men and women, who were exposed to similar occupational exposure including noise, developed CVD in the same degree. However, during their working year's men had approximately double risk to die or suffer from AMI or stroke than women.

2.3.2 Noise and prevalence of CVD outcomes
Many studies (Tomei et al. 2010, Davies et al. 2005) have shown the association of noise exposure with CVD, comprising of MI and CHD. A meta-analysis including 8 studies revealed a significant association of exposure to high noise level with increased risk of CHD mortality and was especially found prevalent in the European population (Miao et al. 2016). The risk for stroke was found to get higher with every 10 dB increase in noise exposure level in elderly people with more than 64.5 years of age due to road traffic noise in the residing area (Sørensen et al. 2011b). The research done in six European countries reported that the aircraft noise exposure for many years might increase the risk for heart disease as well as stroke (Floud et al. 2013). In contrast, some studies that mentioned association of stroke with aircraft noise exposure, the evidence was found to be uncertain due to only a few percentages exposed to high noise level (Huss et al. 2010, Gan et al. 2012).
Annually, diurnal noise exposure levels of $\geq 55$ dB have been thought to cause further 542 cases of MI induced by hypertension and 788 cases of stroke in England (Harding et al. 2013). A small case-control study conducted in Berlin reported that there was a marginal increase in the risk of MI for people who were exposed to street noise greater than 70 dB of sound level residing for at least 15 years in Berlin (Babisch et al. 1994). Increased MI mortality was reported due to increased aircraft noise exposure levels and durations whereas no association was noted with the stroke in a large cohort study conducted in Switzerland (Brook et al. 2004).

2.3.3 Occupational noise and prevalence of CVD outcomes

A systematic literature review by SBU (2015), reported that people who are more exposed to noise in workplace develop heart disease and stroke. A literature review comprising of studies from the year 1981-89, which is also the first of two articles reviewing research on CVD and occupational environment, showed a correlation between exposure to occupational noise and CVD in almost half of the included studies. The quality of the studies gradually increased resulting to increased coherence and supported potential causal relationship (Kristensen 1989). In an in-depth review, a weak association was found between occupational noise and CVD, giving emphasis to conduct more longitudinal research on workplace noise and CVD in future (Skogstad et al. 2016). In addition, subjects exposed to noise level greater than 85 dB(A) for more than 10 years showed no statistically significant result for higher risk of CVD deaths, in an 8 years’ incidence study by Cardiovascular Occupational Risk Factor Determination in Israel (CORDIS) (Melamed et al. 1999).

In a long follow-up study of male workers in industries, the result showed moderate but statistically significant increased CHD risk with occupational noise especially impulse noise even though workers had surpassed their retirement age (Virkkunen et al. 2005). The National Health and Nutrition Examination Survey (NHANES) 1999-2004, revealed that exposure to severe noise was highly associated with the prevalence of CHD mostly in young current male smokers (Gan et al. 2011).

The study by Stokholm et al. (2013), resulted in no association between stroke and exposure to occupational noise. Two occupational groups were taken in the study namely, industrial and financial workers and after adjusting for confounders the risk for stroke increased by 27% for industrial workers than financial workers. The longest duration of noise exposure and high noise
levels were found to be unrelated to stroke risk and explained the possibility of having a higher risk in industrial workers might be due to their different lifestyle patterns. A population-based cohort study by Gopinath et al. (2011) revealed association of workplace noise with CVD. In the study, there was no association between workplace noise exposure and stroke prevalence. When noise exposure level was measured with duration, those who had tolerable noise exposure level of greater than 5 years were highly likely to have prevalent CVD as compared to those unexposed to occupational noise. Similarly, the study (Gopinath et al. 2011) also reported no association with AMI and stroke when analyzed with combined severe noise exposure level and duration. However, a significant association was found in incidence analysis with stroke for severe noise exposure level in less than 5 years, after some variable adjustments.

Most of these previous studies were found to be conducted in men only. Thus, a study NaRoMI (Noise and Risk of Myocardial Infarction) was conducted to explore the association between severe noise exposure with risk for MI in both male and female to measure the risk of perceived personal annoyance and objective noise levels in the environment and workplace. The result of NaRoMI study indicated that severe noise exposure is mild to moderately associated with risk for MI (Willich et al. 2006). Similarly, another study published in the same year among lumber mill workers in British Columbia reported that severe noise exposure levels at workplaces were associated with higher risk for AMI mortality (Davies et al. 2005). The findings of some studies show positive associations between traffic or occupational noise exposure with MI (Babisch et al. 1999, Babisch et al.2005, Babisch 2006, Andersson et al. 2007, Huss et al. 2010). Likewise, another study also showed that occupational noise exposure and work strain increase risk for MI considerably (Selander et al. 2013).

### 2.3.4 Risk factors associated with occupational noise and CVD outcomes

In the words of Virkkunen et al. (2005), the workers tend to smoke or develop bad eating habits due to annoying noise exposure at work. The study also suggests hypertension may be considered as a marker for increased CHD risk. A significant association was found between air traffic noise exposure at work with hypertension in a subsequent meta-analysis (van Kempen et al. 2002). A review article by Stansfeld et al. (2000) revealed an association between occupational noise and hypertension. Similarly, a strong association was found between occupational noise exposure with hypertension (Skogstad et al. 2016). The two large cohort studies by Eriksson et al. (2010) and
Sbihi et al. (2008) showed an increased risk for hypertension with workplace noise. However, a study by Stokholm et al. (2013) reported no association of elevated risk for hypertension with occupational noise exposure in the below half range of 80-90 dB(A). The study results also showed that risk for hypertension does not increase with elevated level of noise in both genders within industrial blue-collar workers. In the study by Davies et al. (2005), smoking was not found to be the confounder for the association between noise and heart disease. The result was found to be quite similar with another study by Suadicani et al. (2012), where there was no difference found between prevalence of smoking and alcohol intake with noise exposure level. However, overall smoking measured as pack-year was little higher among the highest noise exposure level group. Among the group with the prolonged period of noise exposure, the lipid fractions and body mass index (BMI) were found to be very high.

An association between noise annoyance and serum lipid levels regardless of actual noise levels was found in the CORDIS study by Melamed et al. (1997). The study highlights on individual noise annoyance and its relationship with factors for CHD risk. High total cholesterol level, triglyceride level, and cholesterol ratio were found in young men of ≤ 44 years of age exposed to elevated level of noise of ≥ 80 dB(A). On the contrary, no effect was found between noise and serum lipid/lipoprotein levels in women and in older men age greater than 45 years. Noise annoyance differed with total cholesterol level and HDL level in young men. Similarly, noise annoyance varied with total cholesterol, triglyceride, and HDL level in women. Combined effect of noise annoyance and noise exposure levels was seen on cholesterol levels. Young men scoring high on noise annoyance and exposure levels had a 15 mg/dl higher mean cholesterol level than the ones scoring low in both variables, whereas in women the difference was found to be 23 mg/dl.

The results of a prospective 13 years’ follow-up study by Virkkunen et al. (2006), revealed that those exposed to continuous noise and impulse noise were concurrently exposed to high physical workload. Likewise, those exposed to continuous noise were also exposed to both physical workload and shift work. Hence, the study concluded that in the shortest follow-up comprising of some retired workers, workers working in shifts and workers exposed to continuous noise had a higher risk for CHD compared to workers working in longer follow-up with higher number of retired workers. On the contrary, the risk for CHD increased with follow-up time in physical workload and impulse noise.
2.4 Possible biological mechanism

A study by Recio et al. (2016), mentioned noise as a stressor for neuroendocrine system activating the SAM system and increasing the plasma cortisol levels as well as catecholamine levels resulting to CVD with vasoconstriction and increased blood pressure (BP). The study further elaborates on physiological disorders causing cardiovascular episodes and disease disorders in the circulatory system and could be observed by different markers for CVD like BP, blood clotting factors, lipid concentration in blood, inflammation, and variability in heart rate. Some studies (Maschke et al. 2000, Lee et al. 2009) explained the effects of stress in long run by causing psychophysiological changes which further leads to alterations in pathological conditions of central nervous and cardiovascular as well as endocrine systems. The biological mechanism for noise with different markers for CVD based on different studies are explained as follows:

2.4.1 Cardiac physiology and hypertension

In the presence of stressor like noise, heart rate variability (HRV) gives a measurement of joint functions of the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) to regulate cardiac output. The study by Lee et al. (2010), revealed that HRV might be affected by certain noise exposure level by activation of autonomic nervous system (ANS). In the groups with ANS regulatory issues, the markers for HRV are more prone to cardiovascular deaths (Gerritsen et al. 2001). According to Kraus et al. (2013), the diurnal noise increases sympathetic activity and is associated with reduction in HRV for brief period. The case-crossover study on young population conducted by Huang et al. (2013) showed noise level above certain level influenced an increase in effects of air pollution on a variability of heart rate for short term. The research by Graham et al. (2009) reported that the disturbances of environmental noise with sleep cause malfunction of ANS resulting to low heart rate. Recio et al. (2016) suggested that almost all studies (Graham et al. 2009, Griefahn et al. 2008) which experimented the relation of noise at night time with variation in heart rate and cardiac output showed immediate effects after the exposure.

A laboratory study done on human showed high exposure to noise significantly increase BP as recorded in the road traffic noise (Paunovic et al. 2014). Recio et al. (2016), revealed that the vasoconstriction and decreased cardiac output resulted in elevated BP during high noise exposure. Many cross-sectional studies conducted in children (Liu et al. 2014, Belojevic et al. 2008) and adults on road traffic noise and blood pressure have shown significant associations (Sørensen et al.
The meta-analysis by van Kempen and Babisch (2012), found an increase in road traffic noise levels significantly associated with an increase in the risk of prevalence of hypertension. Later a cohort study by Chang et al. (2013), reported a significant association between increased BP and hypertension in men. However, Recio et al. (2016) and Sørensen et al. (2011a) stated that no studies were found to show significant association of road traffic noise and hypertension for the incidence and concluded that there is a possibility of noise in combination with other factors which might cause hypertension.

### 2.4.2 Atherosclerosis

There are many factors related to noise like increased blood lipids, endothelial inflammations and endothelial dysfunction (ED), blood clotting changes and aggregation of platelets which can add to the development of subclinical atherosclerosis or can activate acute cardiovascular episodes (Recio et al. 2016).

According to American Heart Association (2017b), “Atherosclerosis is the process in which deposits of fatty substances, cholesterol, cellular waste products, calcium and other substances build up in the inner lining of an artery”. The deposit is called as plaque. The obstruction in the blood vessel that supplies blood to the brain due to deposition of fatty substance in vessel walls causes the Ischemic stroke.

In certain noise levels, there can be an overproduction of cortisol due to activation of the neuroendocrine system in acute or severe stress and might cause atherosclerosis. Stressful actions produce alterations in the levels of lipid and lipoprotein in male adults (Qureshi et al. 2009). A study conducted in animals reported that lipid peroxidation is caused by acute psychological stress due to oxidative stress in tissues. (Wang et al. 2007). In the study by Mehrdad et al. (2011), no statistical relationship could be found between total cholesterol, HDL and LDL with noise and only after adjusting for variables in the result, triglyceride showed differences between high (> 90 dB) and low (<80 dB) noise exposed groups.

The study by Recio et al. (2016) reported that there is very little research focused on noise and atherogenic markers or no publication of research with non-significant results. On the contrary, after adjusting for air pollutants, a German cohort based by Kälsch et al. (2014), found road traffic noise to be significantly associated with subclinical atherosclerosis.
2.4.3 Inflammation and Endothelial dysfunction (ED)

The biomolecule, endocrine cytokine also known as the interleukin-6 (IL-6), has proinflammatory and procoagulant effects and participate in immunologic activation and neuroendocrine stimulation (Hartman & Frishman 2014). In the studies conducted in animals, proatherogenic effects were shown to be associated with IL-6 (Huber et al. 1999) and studies in healthy humans showed ED related with levels of IL-6 (Esteve et al. 2007). The over secretion of IL-6 enhances the condition of systemic inflammations and might lead to ED causing an imbalance in atherosclerotic plaques (Recio et al. 2016). Likewise, some studies (Bonetti et al. 2003, Libby et al. 2002) indicate that ED plays a key role in the atherosclerotic mechanism.

The study by Recio et al. (2016), revealed that the vascular activities to psychological stress are maintained by the endothelium and that there is much research on the relation between psychological stress and ED with neuroendocrine system dysfunction. A healthy endothelium helps to regulate vascular activities and structure and has anticoagulant, antiplatelet and fibrinolytic functions. Vascular activities are maintained by the discharge of various dilator as well as constrictor substances. Nitric Oxide (NO) is the main vasodilative substance released by endothelium and is called as endothelium-derived relaxing factor (EDRF). The endothelium also releases vasoconstrictor substances like endothelin and angiotensin II (Davignon & Ganz 2004).

Angiotensin II is also pro-oxidant (Sowers 2002) and stimulates the release of endothelin (Davignon & Ganz 2004). Endothelin 1 stimulates at least three signaling pathways in vascular smooth muscle cells. It plays a key role in cellular growth regulation, generation, and survival of vascular smooth muscle cells. The activation of these signaling episodes are abnormal and might lead to development of vascular diseases (Bouallegue et al. 2007.) The stimulated macrophages and vascular smooth muscle cells are the typical cellular elements of atherosclerotic plaque which release a huge amount of endothelin (Kinlay et al. 2001).

As cited in Davignon and Ganz (2004), Ross (1999) stated that ED causes an imbalance between vasoconstriction and vasodilation and begins many episodes which promote atherosclerosis that includes increased permeability of endothelium, platelet aggregation, leukocyte adhesion, and release of cytokines. The study also mentioned that due to impaired vasodilation there may be decreased production and performance of NO which may be considered as the earliest indication of atherosclerosis.
There is evidence that noise, considered as a psychological stressor was responsible for lesions in endothelium and malfunctions for short duration (Recio et al. 2016). The study by Widlansky et al. (2003) gives more insight about the association between increased BP and noise with arteriosclerosis and hypertension through a damaged vascular structure. The study reveals that several vascular alterations are associated with ED like a decrease in vasodilatation, progression of prothrombotic and proinflammatory stage and proliferation of smooth muscle cell, which leads to the development of atherosclerotic lesions. Subjects with weak endothelial function have a higher risk of adverse cardiovascular episodes in comparison to subjects with normal endothelial function (Gokce et al. 2002, Heitzer et al. 2001, Perticone et al. 2001). In another study, it was reported that there may be permanent vascular effects due to transportation and occupational noise exposure (Babisch 2006).

A repeated measure study conducted in adults on the exposure to noise and 24 hours’ ambulatory vascular structural properties concluded that environmental exposure to noise may have short or long-term effects on vascular structural properties (Chang et al. 2012). According to the study by Schmidt et al. (2013), exposure to more chronic noise leads to more ED. In the study, it is reported that hypertension may be the result of hormones like epinephrine and nor-epinephrine due to stress exerted by noise and the progression of ED.

As mentioned by Davignon and Ganz (2004), ED is regarded as an initial indicator for atherosclerosis giving angiographic or ultrasonic proof of atherosclerotic plaques and is a characteristic trait for the patient with coronary atherosclerosis. Some studies suggest that it may foretell long-term development of atherosclerosis and cardiovascular event rate (Suwaidi et al. 2000).

The homeostasis of endothelium is adversely affected by the risk factors for CVD leading to atherosclerosis. The interruption in endothelial homeostasis may also be due to other environmental factors like genetic or lifestyle factors. Hence, changes in endothelial functions can act as a barometer for cardiovascular risk (Widlansky et al. 2003).
Oxidative stress is defined as "a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses" (Betteridge 2000). Recio et al. (2016), reported that activation of the neuroendocrine system and increased IL-6 production can enhance systemic oxidative stress. The research was done in animal (Koc et al. 2015) and human (Yildirim et al. 2007) indicated high exposure to noise associated with markers of elevated oxidative stress.

Classical risk factors:
- Diabetes Mellitus
- Smoking
- Hypertension
- Ageing
- Dyslipidemia

Novel/Emerging risk factors:
- Infection/Inflammation
- Physical inactivity
- Obesity
- Homocysteine
- Post-prandial state

Intrinsic susceptibility - genetic and environmental factors

ENDOTHELIAL DYSFUNCTION
- Impaired vasomotion/tone
- Prothrombotic state
- Proinflammatory state
- Proliferation in arterial wall

Atherosclerotic Lesion Formation and Progression
- Plaque Activation/ Rupture
- Decreased Blood Flow due to Thrombosis and Vasospasm

Cardiovascular Disease Events

Figure 1. Endothelial dysfunction and its pathogenesis of cardiovascular disease (CVD) (Modified from Widlansky et al. 2003).
2.4.4 Diabetes
The increase in blood glucose levels hardens the arteries with the rise in BP and viscosity causing increased risk of blood clotting. The consequences of elevated blood glucose level with dyslipidemia and risk factors for CVD increases the risk for ischemic heart disease (IHD) as well as CVD (Kannel 2011). A long-term association was found in Sørensen et al. (2013) study between diabetes (Type 2) and road traffic noise resulted that during past 5 years, for every 10 dB rise in noise levels caused 11% increased the risk of incident type 2 diabetes. Likewise, another study of the short-term association of Type 2 diabetes and noise showed significant association where an increase in 0.5 dB(A) noise at night time was related with 4.6% increased the risk of diabetic deaths in following day (Tobías et al. 2015). The pathways for type 2 diabetes caused by noise might be due to the excess production of glucocorticoids like cortisol which is released in presence of stressors like noise exposure at elevated levels, causing reduced secretion of pancreatic insulin and decline of insulin sensitivity in liver, the muscle of skeletal system as well as in adipose tissues. The changes in glucose and eating adjustments were associated with sleep disturbances that may be due to environmental noise (Sørensen et al. 2013, Tasali et al. 2009).

2.4.5 Sleep deprivation and air pollution
Disturbance in sleep plays a key role in CVD pathway and an acute or chronic disruption in sleep is found to be associated with poor pancreatic insulin secretion (Buxton et al. 2012), reduced insulin sensitivity (Buxton et al. 2010), alterations of hormones in appetite regulation (Taheri et al. 2004) and rise in sympathetic tone and venous ED (Dettoni et al. 2012). From the epidemiological studies, it was found that sleep less than 6 hours per night was associated with many physiological conditions like obesity (Patel & Hu 2008, Knutson & van Cauter 2008), diabetes (Knutson & van Cauter 2008, Beihl et al. 2009), hypertension (Wang et al. 2012), CVD (Shankar et al. 2008) and all-cause mortality (Gallicchio & Kalesan 2009, Cappuccio et al. 2010).

The WHO report in 2012 mentioned that air pollution contributed to 6.7% of total global deaths and was the cause of 29% of heart disease and stoke deaths (Lee et al. 2014). The studies conducted in the US and Europe revealed that the particulate matter \((\text{PM}_{10})\) showed a close relationship between air pollution and CVD (Brook et al. 2003, Zanobetti et al. 2003, Brook 2008). Studies have reported that every 10 µg/m³ level elevations in \(\text{PM}_{10}\) showed corresponding increase of 0.7%
of IHD hospitalization and 0.8% of congestive heart failure hospitalization (Morris 2001). Similarly, the association between air pollution (PM$_{10}$) and stroke was also reported in the US (Low et al 2006). The air pollution leads to CVD via oxidative stress and inflammation (van Eden et al. 2001). Noise and air pollution is highly correlated in road traffic studies and are causally associated with CVD. Traffic air pollution might act as a confounder in traffic noise and CVD association and vice versa (Foraster et al. 2011).

Figure 1. Biological mechanism of noise exposure for the risk of cardiovascular disease (CVD) (Modified from Recio et al. 2016).
Although many studies have shown the associations between environmental noise and CVD outcomes, very few studies were found to be focused on occupational noise exposure and CVD outcomes. Only handful of studies researched on occupational noise with CHD deaths, stroke deaths and AMI. Additionally, many of those limited studies had inconsistent results. Thus, the need to study these associations cannot be ignored. The KIHD study comprises of information on occupational noise exposure from the participants and data on CVD outcomes and deaths. Therefore, our study utilizes the KIHD information and seeks to explore the associations between occupational noise exposure and CVD outcomes (CHD deaths, stroke deaths and AMI).
3. AIMS OF THE STUDY

3.1 General aim
The general aim of this study is to determine the association between occupational noise exposure and risk for cardiovascular deaths (CHD deaths, stroke deaths) and AMI.

3.2 Specific aims
1. To measure the risk for CHD deaths, stroke deaths and AMI between occupational noise exposure group (unexposed and exposed).
2. To assess the risk for CHD deaths, stroke deaths and AMI with noise-years.
4. MATERIALS AND METHODS

4.1 Kuopio Ischemic Heart Disease Risk Factor Study
The Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) is a large ongoing population based epidemiological longitudinal follow-up study. It is designed to explore risk factors for CVD outcomes and other similar outcomes. In the baseline study (1984-1989), 2682 men of age group 42-60 years were recruited from the Eastern part of Finland in two cohorts. The first cohort (1984-1986) comprised of 1166 men of 54 years of age and the second cohort (1986-1989) comprised of 1516 men with the age group 42-60 years. The monitoring of the baseline examinations was done by 4-year examination round from 1991-1993 where around 88% of the eligible participants (1038 men) from the second cohort participated for the examinations. For the 11-year examination round from 1998-2001, 95% eligible participants (854 men) participated from second cohort. Likewise, for the 20 years’ examination round, all the eligible participants were invited from the two cohorts (Salonen 1988, Yary et al. 2017) where 1875 men participated (Aregbesola 2016).

4.2 Sample
The participants for the study were men from the baseline first and second cohorts who belonged to different occupational groups; farmers, blue-collar workers (work in the field requiring physical strength) and white-collar workers (work in the field requiring mental strength) from the KIHD baseline study. Out of 2682 participants, a total of 2130 participants were included in the study based on the availability of data on occupation, exposures and outcomes.

4.3 Description of data
4.3.1 Data collection
The participants of the study completed three sets of questionnaires that were mailed to the participants and clinical examinations were performed in the study center. The participants were interviewed by the research nurse in the clinical examination where blood samples were also collected.

4.3.2 Assessment of occupational noise exposure
Participants reported occupational noise exposure, the level of noise they perceived in their current and longest jobs and the duration of longest lasting job in the self-administered questionnaire at the baseline. The participants were categorized into noise unexposed and exposed groups and these
groups were placed together in a new exposure variable “noise exposure group”. The participants belonging to unexposed groups were not exposed to noise in their current as well as the longest job. In contrast, noise exposed group comprised of participants who were exposed to noise in their longest job. A ten-point Likert scale was used from “very quiet” to “very noisy” to measure perceived level of noise by noise-exposed participants in the longest job. The noise level perceived by the participants were multiplied to the duration of their longest job to get “noise-years” as the exposure variable. Noise-years represents the total noise levels which the participants experienced throughout their job duration.

4.3.3 Assessment of covariates
The covariates for the study were selected based on literature supporting the association for noise with CVD. The covariates include age, date of examination (the date at which baseline examinations; filling up questionnaires and clinical examinations were completed), socio-economic factors, biological and behavioral factors from baseline study questionnaire. The data on age, smoking, alcohol consumption, occupational group, job shift and IHD history were obtained from self-administered questionnaire.

The behavioral factors for this study were smoking and alcohol consumption. Smoker was defined based on history of smoking on regular basis or had smoked cigarette, cigars, or a pipe within the past 30 days. The “pack-years” for the cigarettes was calculated by multiplying the years of smoking the tobacco products with the number of tobacco products smoked daily at the examination time. The years of smoking was defined as the total number of years of smoking irrespective of start of smoking, or cessation of smoking or had smoked continuously or smoking in several periods (Salonen et al. 1992). Alcohol consumption was calculated based on frequency and amount of drinks (beer, wine, and spirits) consumed on each occasion for the past 12 months and was measured in grams per week (Wang et al. 2016).

Likewise, the socio-economic factors for this study comprised of occupational group and job shift. The occupational group was classified as farmers, blue-collar workers and white-collar workers (Harper et al. 2002). This occupational group was further merged into blue-collar and white-collar workers for the convenience of the analysis. A binary variable was created for job shift which classified participants in the standard work shift and non-standard work shift based on a previous article by Wang et al. (2016) with minor modifications. In the standard work shift, the participants
working on weekdays during daytime for less than or equal to 5 days were categorized and the rest of the participants working more than 5 days or in any shifts (evening, night or day) were categorized in non-standard work shift group.

The biological factors comprised cholesterol levels, BMI and BP. The data on HDL cholesterol, LDL cholesterol, total serum cholesterol was determined from collected blood samples for the baseline KIHD study. The cholesterol levels were measured in mmol/L and BMI in weight/height$^2$ (kg/m$^2$) based on the baseline data. The resting BP was measured by a nurse on the initial day of examination in mm Hg. The final systolic blood pressure (SBP) and diastolic blood pressure (DBP) was measured by the overall mean of 6 measurements which is 3 supines, 1 standing and 2 sitting (Salonen et al. 1992).

The prevalent IHD was defined as those subjects who had the history of MI or angina pectoris or positive angina pectoris based on the London School of Hygiene interview (Rose et al. 1982, Salonen et al. 1992). The participants with pre-existing CHD, stroke and AMI were not excluded from the study. Hence, to minimize the confounding effect and get more accurate results IHD history was selected as a covariate.

### 4.3.4 Assessment of outcome variables

The three outcome variables for this study were CHD deaths, stroke deaths, and AMI. Each of the outcomes has binary categories of “Yes” and “No”. The CHD deaths and stroke deaths were measured from National Death Registry by using Finnish personal identification codes (Laukkanen et al. 2006). For the AMI during follow-up, the data was extracted from the record linkage with national hospitalization discharge registries that included national AMI register which was established under the WHO’s Monitoring of Trends and Determinants of Cardiovascular Diseases (MONICA) (Pedoe et al. 1994, Tuomilehto et al. 1992). The CHD deaths (I20-I25), stroke deaths (I60 –I64) and AMI (I20-I22) were coded according to International classification of diseases (ICD) (Kurl et al. 2006).

### 4.4 Statistical analysis

All statistical analysis was performed using SPSS software version 20.0. At first, descriptive analysis was conducted to find out the distribution of noise exposure group (unexposed and exposed). All the continuous and categorical variables were divided into noise exposure group
where the continuous variables were presented in mean and standard deviation (SD) and categorical variables in numbers and percentages. All continuous variables were not normally distributed. Thus, p-values for all the continuous variables were calculated using Mann-Whitney U test. The p-values for all categorical variables were calculated using Spearman test.

The missing values of continuous variables like smoking, alcohol, LDL cholesterol, HDL cholesterol, total serum cholesterol, BMI, mean SBP and mean DBP were less than 5%. These missing values were replaced by using mean values of each variables. In the case of "noise-years", it only comprised of those participants who were exposed to noise in their longest job duration. Therefore, the overall missing values for the noise-years is more than 40% due to the combined missing values of those exposed to noise in their current job and those who were not at all exposed to noise. Thus, the original missing values for noise-years is less than 5% which was solely from those participants who were exposed to noise in their longest job. No missing values were replaced by its mean value in noise-years. Similarly, the missing values were not replaced in categorical variables like the occupational group and job shift where the missing values were also less than 5%.

To find out the association between exposures (noise exposure group and noise-years) with the outcomes (CHD deaths, stroke deaths, and AMI) separately, the possible confounding effects were taken into consideration. Analyses were performed to examine the confounding criteria to observe causal model pathway between exposures and outcomes. The criteria for confounding must be met for a variable to be a confounder and it must have significant association with the outcome that is independent of the exposure. The potential confounder should not lie in the causal pathway between exposure and outcome and it must be significantly associated with the exposure. The list of exposures, outcomes and possible confounders are presented in Table 1.
Table 1. List of exposures, outcomes and possible confounder variables.

<table>
<thead>
<tr>
<th>Dependent Variables (Exposures)</th>
<th>Outcome variables</th>
<th>Possible confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noise exposure group (unexposed/exposed)</td>
<td>CHD deaths</td>
<td>Age, y</td>
</tr>
<tr>
<td>Noise-years</td>
<td>Stroke deaths</td>
<td>Smoking, pack-years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alcohol, g/week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDL cholesterol, mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HDL cholesterol, mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total serum cholesterol, mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean SBP, mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean DBP, mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occupational group, Blue/White</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Job shift, standard/non-standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IHD history, Yes/No</td>
</tr>
</tbody>
</table>

At first, to measure the association between exposures and confounders, correlation analysis was performed for each confounder with the exposures. Kolmogorov-Smirnov test was used to check the normality of continuous variables. All the continuous variables were not normally distributed. Thus, Spearman correlation was used to check the correlation between each possible confounder with each exposure (noise exposure group and noise-years). A cut-off points of p-value <0.2 was taken to select confounders for noise exposure group. In contrast, a cut-off points of p-value <0.1 was taken to select confounders for noise-years. The cut-off point range for noise exposure group was higher by additional 0.1 than the noise-years to compensate those real values that were lost due to grouping for noise unexposed and exposed categories in noise exposure group. Likewise, to measure the association of possible confounders with the outcomes (CHD deaths, stroke deaths, and AMI), binary logistic regression was used individually with each outcome with cut-off point of p-value <0.1.

The covariates that fulfilled the criteria of confounder for noise exposure group (p-value <0.2) with the outcomes (p-value <0.1) are listed in Table 2.
Table 2. Confounders for the association of noise exposure group with the outcomes.

<table>
<thead>
<tr>
<th>CHD deaths</th>
<th>Stroke deaths</th>
<th>AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td>Alcohol</td>
<td>IHD history</td>
<td>IHD history</td>
</tr>
<tr>
<td>IHD history</td>
<td>Occupational group</td>
<td></td>
</tr>
<tr>
<td>Occupational group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Job shift</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The covariates that fulfilled the criteria of confounder for noise-years (p-value<0.1) with the outcomes (p-value <0.1) are listed in Table 3.

Table 3. Confounders for the association of noise-years with the outcomes.

<table>
<thead>
<tr>
<th>CHD deaths</th>
<th>Stroke deaths</th>
<th>AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Mean SBP</td>
<td>HDL cholesterol</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>Mean SBP</td>
<td></td>
</tr>
<tr>
<td>Mean SBP</td>
<td>Occupational group</td>
<td></td>
</tr>
<tr>
<td>Occupational group</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lastly, after selecting confounders, Cox Regression analysis (Proportional Hazard analysis) was performed to get hazard ratio at 95% CI for each exposure with the outcomes where the confounders were adjusted.

4.5 Ethical consideration

Approval was taken from Research Ethics Committee of the University of Kuopio for the KIHD study protocol. Written informed consent for participation was taken from all subjects. The confidentiality of all collected information was ensured.
5. RESULTS

5.1 Characteristics of study population

The baseline characteristics of the study participants based on noise exposure group (unexposed and exposed groups) are presented in Table 4. The basic characteristics of continuous variables are represented in the first half of the table in mean (SD) and of the categorical variables are represented in the second half in N (%). In total of 2130 participants, 951 were unexposed and 1179 were exposed to occupational noise.

The mean age of participants in unexposed group was 52.9 years and in exposed was 53.2 years with the age range from 42 to 61.33 years. There were no significant differences in the first half of the table with continuous variables. On the contrary, in the second half of the table, significant differences were observed in the categorical variables; occupational group (p-value <0.001), job shift (p-value = 0.002) and IHD history (p-value = 0.010) with noise exposure group. Among the exposed group, majority of the blue-collar workers (75.7%) were found to be exposed to occupational noise. Likewise, more than half of the workers in exposed group were workers working in standard working hours (59.9%) and very few workers (25.4%) among exposed group reported history of IHD.
Table 4. Study population characteristics based on noise exposure group (N=2130).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unexposed (N=951)</th>
<th>Exposed (N=1179)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52.9±5.1</td>
<td>53.2±5.2</td>
<td>0.112</td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>7.5±15.5</td>
<td>7.9±15.8</td>
<td>0.795</td>
</tr>
<tr>
<td>Alcohol, g/week</td>
<td>70.8±102.7</td>
<td>71.5±120.6</td>
<td>0.162</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>4.04±0.99</td>
<td>4.00±0.99</td>
<td>0.408</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.29±0.30</td>
<td>1.30±0.30</td>
<td>0.440</td>
</tr>
<tr>
<td>Total serum cholesterol, mmol/L</td>
<td>5.89±1.04</td>
<td>5.88±1.09</td>
<td>0.700</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.66±3.51</td>
<td>26.86±3.51</td>
<td>0.207</td>
</tr>
<tr>
<td>Mean SBP, mmHg</td>
<td>134±17</td>
<td>134±16</td>
<td>0.295</td>
</tr>
<tr>
<td>Mean DBP, mmHg</td>
<td>88±10.24</td>
<td>89±10.33</td>
<td>0.353</td>
</tr>
<tr>
<td>Occupational group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blue</td>
<td>338 (36.0)</td>
<td>877 (75.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>602 (64.0)</td>
<td>281 (24.3)</td>
<td></td>
</tr>
<tr>
<td>Job shift</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>629 (66.4)</td>
<td>703 (59.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Non-standard</td>
<td>319 (33.6)</td>
<td>471 (40.1)</td>
<td></td>
</tr>
<tr>
<td>IHD history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>196 (20.6)</td>
<td>299 (25.4)</td>
<td>0.010</td>
</tr>
<tr>
<td>No</td>
<td>755 (79.4)</td>
<td>880 (74.6)</td>
<td></td>
</tr>
<tr>
<td>CHD deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>137 (14.4)</td>
<td>178 (15.1)</td>
<td>0.655</td>
</tr>
<tr>
<td>No</td>
<td>814 (85.6)</td>
<td>1001 (84.9)</td>
<td></td>
</tr>
<tr>
<td>Stroke deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29 (3.0)</td>
<td>39 (3.3)</td>
<td>0.736</td>
</tr>
<tr>
<td>No</td>
<td>922 (97.0)</td>
<td>1140 (96.7)</td>
<td></td>
</tr>
<tr>
<td>AMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>280 (29.4)</td>
<td>371 (31.5)</td>
<td>0.313</td>
</tr>
<tr>
<td>No</td>
<td>671 (70.6)</td>
<td>808 (68.5)</td>
<td></td>
</tr>
</tbody>
</table>

1 mean±SD, 2 N (%), 3 Mann-Whitney U test, 4 Spearmen test

LDL, low-density lipoprotein; HDL, High-density lipoprotein; BMI, body mass index; SBP, systolic blood pressure; DBP diastolic blood pressure; IHD, ischemic heart disease; CHD, coronary heart disease; AMI, acute myocardial infarction
5.2 Analysis of exposures with possible confounders

Spearman correlation was performed in Table 5 to find the relationship between the two exposures (noise exposure group and noise-years) with possible confounders. The cut-off points for noise exposure group was <0.2 and for noise-year was <0.1.

The noise exposure group was found to be significantly correlated with age (p-value= 0.112), alcohol (p-value= 0.162), occupational group (p-value <0.001), job shift (p-value= 0.002) and IHD history (p-value= 0.010) at cut-off point of p-value <0.2. Likewise, age (p-value <0.001), alcohol (p-value= 0.004), HDL cholesterol (p-value= 0.002), mean SBP (p-value=0.009) and occupational group (p-value <0.001) were significantly correlated with noise-years at p-value <0.1 as cut-off point.

Table 5. Spearman correlation between exposures and possible confounders

<table>
<thead>
<tr>
<th>Variables</th>
<th>Noise exposure group p-value</th>
<th>Noise-years p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>0.112</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>0.525</td>
<td>0.783</td>
</tr>
<tr>
<td>Alcohol, g/week</td>
<td>0.162</td>
<td>0.004</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>0.408</td>
<td>0.549</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>0.440</td>
<td>0.002</td>
</tr>
<tr>
<td>Total serum cholesterol, mmol/L</td>
<td>0.700</td>
<td>0.107</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.207</td>
<td>0.233</td>
</tr>
<tr>
<td>Mean SBP, mmHg</td>
<td>0.295</td>
<td>0.009</td>
</tr>
<tr>
<td>Mean DBP, mmHg</td>
<td>0.353</td>
<td>0.664</td>
</tr>
<tr>
<td>Occupational group</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Job shift</td>
<td>0.002</td>
<td>0.855</td>
</tr>
<tr>
<td>IHD history</td>
<td>0.010</td>
<td>0.323</td>
</tr>
</tbody>
</table>

LDL, low-density lipoprotein; HDL, High-density lipoprotein; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; IHD, ischemic heart disease
### 5.3 Analysis of outcomes with possible confounders

The analysis for measuring associations between possible confounders with the outcomes (CHD deaths, stroke deaths and AMI) are depicted in Table 6. The cut-off point for all three outcomes were taken at p-value <0.1.

All the variables were significantly associated with CHD deaths except job shift. Likewise, age (p-value= 0.016), BMI (p-value= 0.057), mean SBP (p-value <0.001) and mean DBP (p-value <0.001) were found to be significantly associated with stroke deaths. Except alcohol and job shift all the variables showed statistically significant associations with AMI.

Table 6. Binary logistic regression analysis between outcomes and possible confounders

<table>
<thead>
<tr>
<th>Variables</th>
<th>CHD deaths</th>
<th>Stroke deaths</th>
<th>AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td>Age, y</td>
<td>&lt;0.001</td>
<td>0.016</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>&lt;0.001</td>
<td>0.549</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol, g/week</td>
<td>0.007</td>
<td>0.898</td>
<td>0.581</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>&lt;0.001</td>
<td>0.906</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>&lt;0.001</td>
<td>0.876</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total serum cholesterol, mmol/L</td>
<td>&lt;0.001</td>
<td>0.110</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>&lt;0.001</td>
<td>0.057</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean SBP, mmHg</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean DBP, mmHg</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>Occupational group</td>
<td>&lt;0.001</td>
<td>0.763</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Job shift</td>
<td>0.147</td>
<td>0.809</td>
<td>0.380</td>
</tr>
<tr>
<td>IHD history</td>
<td>&lt;0.001</td>
<td>0.132</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LDL, low-density lipoprotein; HDL, High-density lipoprotein; BMI, body mass index; SBP, systolic blood pressure; DBP diastolic blood pressure; IHD, ischemic heart disease
5.4 Association between noise and outcomes

The associations between noise and the outcomes of the study are presented in Table 7 and Table 8. Table 7 represents the association between noise exposure groups with the outcomes; CHD deaths, stroke deaths and AMI where unexposed group was taken as the reference group for the analysis. The table comprises of four models; model 1 was adjusted for age and date of examination; model 2\textsuperscript{a} included model 1 components together with alcohol, IHD history, occupational group and job shift; model 2\textsuperscript{b} comprised of model 1 components and IHD history; model 2\textsuperscript{c} had model 1 covariates with IHD history and occupational group. No statistically significant results were obtained between noise exposed groups with all the three outcomes as found in Table 7.

The association between noise-years with the outcomes; CHD deaths, stroke deaths and AMI are depicted in Table 8. The table also has four models; model 1 was adjusted for age and date of examination; model 2\textsuperscript{d} adjusted for model 1 covariates together with alcohol, HDL cholesterol, mean SBP and occupational group; model 2\textsuperscript{e} comprised of model 1 components and mean SBP; model 2\textsuperscript{f} had model 1 variables with additional components, HDL cholesterol, mean SBP and occupational group. Based on the analysis in Table 8, noise-years was not found to be significantly associated with CHD deaths, stroke deaths and AMI.
<table>
<thead>
<tr>
<th></th>
<th>CHD deaths</th>
<th>Stroke deaths</th>
<th>AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.05 (0.84,1.32)</td>
<td>0.651</td>
<td>1.09 (0.68,1.77)</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.88 (0.69,1.12)</td>
<td>0.305</td>
<td>1.08 (0.66,1.74)</td>
</tr>
</tbody>
</table>

Model 1, adjusted for age and date of examination
Model 2\(^a\), adjusted for Model 1 plus alcohol (g/week), IHD history, occupational group and job shift
Model 2\(^b\), adjusted for Model 1 plus IHD history
Model 2\(^c\), adjusted for Model 1 plus IHD history and occupational group
Table 8. Hazard ratio (95% CI) of noise-years with the outcomes

<table>
<thead>
<tr>
<th></th>
<th>CHD deaths</th>
<th></th>
<th>Stroke deaths</th>
<th></th>
<th>AMI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.00 (0.99,1.00)</td>
<td>0.565</td>
<td>1.00 (0.99,1.01)</td>
<td>0.833</td>
<td>1.00 (0.99,1.00)</td>
<td>0.857</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.00 (0.99,1.00)(^d)</td>
<td>0.987(^d)</td>
<td>1.00 (0.99-1.01)(^e)</td>
<td>0.816(^e)</td>
<td>1.00 (0.99,1.00)(^f)</td>
<td>1.00(^f)</td>
</tr>
</tbody>
</table>

Model 1, adjusted for age and date of examination

Model 2\(^d\), adjusted for Model 1 plus alcohol (g/week), HDL cholesterol (mmol/L), mean SBP (mmHg) and occupational group

Model 2\(^e\), adjusted for Model 1 plus mean SBP (mmHg)

Model 2\(^f\), adjusted for Model 1 plus HDL cholesterol (mmol/L), mean SBP (mmHg) and occupational group
6. DISCUSSION

6.1 Summary of principal findings
Noise exposure group and noise-years were not found to be significantly associated with CHD deaths, stroke deaths and AMI, even after adjusting for the confounders. The results of noise-years showing no association with the outcomes are novel findings of this study.

6.2 Comparison with literature
There are many studies analyzing association between noise with CVD but very few studies exploring association between noise exposure with CHD deaths, stroke deaths and stroke incident. Additionally, most of the studies on noise were done in environmental or community noise exposures and very few in occupational settings.

Even after adjusting for the confounders, there were no significant associations seen between two exposures with CHD deaths. Similar result was reported in the study by Guzejev et al. (2007), where environmental noise sensitivity analysis was performed with CVD and adjustments were made for confounders among men and women. No association was found for noise sensitivity with CHD deaths in both sexes. In contrast, when lifetime noise exposure was taken in consideration in age adjusted model, the risk of CHD deaths increased (HR= 3.11; 95% CI= 1.19, 8.10) among noise sensitive women who were exposed to noise. However, the result remained unchanged for men with no significant association. The result was similar for men in both cases when lifetime noise exposure was included and was not included in noise sensitivity analysis with CHD deaths. The use of hearing protective device was not considered in our study and in the study by Guzejev et al. (2007), which might have resulted in similar findings with no association for noise exposure with CHD deaths. The absence of information on use of hearing protective device might cause problem of recall bias which would have influenced the participants’ answer for their noise sensitivity. Nevertheless, the noise sensitivity might vary individually as unlike others, some could be highly sensitive to noise. The study by Guzejev et al. (2007) and our study used Finnish adults as study population. In addition, the questions were also self-reported by the participants like in our study. However, the study was not completely based on occupational noise setting and the exposures were little different from what we used for this study. Thus, the result cannot be regarded as completely comparable.
Another research by Gan et al. (2012) reported that a 10-dB(A) elevation in continuous noise levels increased the risk of CHD deaths (HR=1.26, 95% CI= 1.17, 1.35) in unadjusted model. Later, in adjusted model, the risk of CHD deaths was still seen to be high with 10-dB(A) increase in noise levels. Likewise, in the same study the participants were divided into four categories based on noise deciles and showed increased risk of CHD deaths in higher noise decile categories compared with lower noise decile category. In contrast, we only used perceived noise level for our analysis which was later multiplied with job duration to get noise-years. Noise-years was neither divided in any categories nor was compared with CHD deaths with each increment in noise-years. In addition, the study by Gan et al. (2012) was done in a Canadian community noise exposure and considered only 5 years’ duration of noise exposure whereas our study is done in a Finnish occupational setting with duration of noise exposure ranging from 2-48 years. However, when comparing only the basic concept of noise exposure and risk of CHD deaths, the association was found to be dissimilar. Likewise, another community level study on aircraft noise in France also showed positive association between aircraft noise and CHD deaths even after adjusting for air pollution (Evrard et al. 2015). The reasons for the contrasting results in both studies compared with our study might be due to the difference in study settings, use of dB(A) for analysis of continuous noise level, not being a gender specific study and the possibility of ecological bias with residual effect of confounder. The potential effect of sleep deprivation due to aircraft noise on CVD could not be ignored where sleep deprivation could have acted as a confounder for the positive association of noise with CHD deaths. Likewise, in the case of community noise exposure, sleep deprivation could have played an essential confounding role for the increased risk of CHD deaths.

A study by Virkkunen et al. (2005), conducted in Finnish middle-aged men working in industry, reported that exposure to noise (continuous and impulse noise), especially impulse noise showed moderate but significant association with increased CHD risk even if the workers passed their retirement age. The data for noise were collected qualitatively and exposure for continuous and impulse noise were divided into exposed and unexposed group. Looking at the fundamentals, the covariates taken for adjustments were similar with the covariates of our study. The outcome of interest differed as instead of CHD deaths CHD risk has been studied by Virkkunen et al. (2005). Hence, the result is not completely comparable but gives us an idea that even the qualitative noise exposure could be associated with CHD risk and gives us indication that it might be associated
with CHD deaths in occupational setting. Likewise, another self-reported study by Gan et al. (2011) resulted that severe noise exposure in workplace was strongly associated with prevalence of CHD.

In a Danish study (Stokholm et al. 2013), blue-collar industrial workers were compared with white-collar financial workers for noise exposure in work settings where 27% higher relative risk for stroke was seen among industrial workers than financial workers in adjusted model. In the cumulative noise exposure analysis, the relative risk of stroke increased by 8-fold for the highest exposed group in crude analysis. However, no significant association was observed in the highest exposed group with stroke after adjusting for confounders. The current noise exposure level at >80 dB(A) resulted to increased stroke risk with weak association when industrial workers were compared with financial workers. However, no association was found with stroke incidence at >80 dB(A) when analyzed only in industrial workers. When comparing with the Danish study, we have similar exposure where noise-years were used instead of dB(A)-year, the duration of exposure was used starting from 2 years and did not separate workers using hearing protective device. In contrast, all the male workers (blue-collars and white-collars), noise exposed and unexposed workers were included in our study. The outcome of interest for the study differed as we focused on stroke deaths. However, the Danish study showed a mixed result and concluded in their study that no association could be confirmed for longest occupational noise exposure with stroke. Nevertheless, our study showed a consistent result where the noise exposure group and noise-years showed no significant associations in adjusted models. Hence, this gives us insight to explore further analysis in stroke and stroke deaths to confirm the association. Nevertheless, due to the differences in the findings, the results could not be fully comparable.

In a study of aircraft noise and hospital admissions for CVD and CVD deaths in neighborhood area of Heathrow airport of London (Hansell et al. 2013), a multiple adjusted model was used to show association between aircraft noise and stroke deaths. The relative risk of stroke deaths in day time and night time were found to be increased in noise exposure groups greater than 50 dB. Similarly, the study suggested that the analysis using same exposures for day time and night time noise resulted higher relative risk in night time noise for stroke mortality but the trend analysis with fully adjusted models did not show association for stroke mortality. Other than the trend analysis the results of Heathrow study was conflicting with our study results. The results might have differed due to the choice of analysis, study setting, study population, the use of dB for analysis and the
confounding effect of sleep deprivation on stroke deaths. In contrast, the similarity for the trend analysis with our analysis might be due to the large study population with no data for use of hearing protective device. Additionally, a recent study on aircraft noise in France by Evrard et al. (2015), reported a weak association between stroke deaths and aircraft noise.

There are other studies which have shown a statistically significant association of stroke with road traffic noise (Sørensen et al. 2011b, Floud et al. 2013, Sørensen et al. 2014). The potential confounding effect of air particles for the significant association of noise with stroke should be considered for road traffic noise studies. These studies give insight to investigate association between noise with stroke deaths and in future could be extended to study associations between stroke deaths with occupational noise.

A study conducted in Stockholm, Sweden reported an increase in risk of MI with weak association in occupational noise exposed participants. The occupational noise exposure was measured using the participant’s occupational history and Job-Exposure Matrix (JEM) (Selander et al. 2013). The result was found to be slightly contrasting but somehow relatable. The analysis of our study lacks the use of JEM, despite using JEM by the Stockholm study there was still no strong association seen with MI.

As mentioned in the study by Willich et al. (2006), the occupational noise annoyance was not associated with MI in both unadjusted and adjusted models. Like our study analysis, Willich et al. (2006) used 5-point Likert scale for measuring noise annoyance but they only considered recent 10 years for noise annoyance. On the contrary to our study, Willich et al. (2006) adjusted for ear protection gear. The study result was found to be similar with our study findings and the exposure assessment also used Likert scale. However, adjustment for the use of hearing protection device was lacking in our study. A much older study by Ising et al. (1999), reported MI to be associated with subjective noise at workplace. The method was quite different as the study used Population Attributable Risk (PAR) percentage and duration of exposure to noise which we did not consider in our study. Hence, the association might have occurred due to misclassification of exposure. Additionally, there are many other studies which show statistically significant association between AMI and traffic noise (Selander et al. 2009, Babisch et al. 2005). Nevertheless, the confounding effect of air particles should be considered for the significant association of road traffic noise with AMI. Likewise, in a work setting of Columbia, Canada, severe noise exposure was associated with
AMI deaths (Davies et al. 2005) which gives us understanding for potential association between occupational noise and AMI.

In short, the results of our study could not be fully compared with the previous studies due to lack of literature in the interested outcomes, exposures and differences in study settings and statistical analysis. Additionally, many studies were not conducted in occupational settings. However, the previous studies showed inconsistent results where few were supportive and few were conflicting with our study results.

6.3 Strengths and limitations of the study

The strength of this study includes a prospective study population with large sample size, good follow-up and reliable data. The data for the outcome variables were retrieved from National Hospital Discharge Registry, the National Causes of Death Registry and FINMONICA (Finnish Monitoring of Trends and Determinants of Cardiovascular Diseases) registry which are highly authentic sources. The data on biological factors like BMI and blood pressure (SBP and DBP) were measured for each participant. Likewise, cholesterol (HDL, LDL and total serum cholesterol) was determined from collected blood samples. These measurements of biological factors help in increasing the accuracy of this study. Additionally, self-reported noise has been used as exposure in previous studies to measure association between noise and CVD outcomes (Virkkunen et al. 2005, Guzejev et al. 2007, Gan et al. 2011) which can be considered as the validity for this study. Similarly, use of Likert scale was successful in the studies (Willich et al. 2006, Beach et al. 2011) to measure noise levels; thus, considering it as a strength for the validity and reliability of this study.

There are some limitations of this study which needs special attention. We did not include female population; thus, the results cannot be generalized. Additionally, hearing protective device was not considered. Nevertheless, there could be possibility for recall bias as the participant might fail to recall the use of hearing protective device when reporting for the noise level. Even though, self-reported noise has been used in previous studies, some problems associated with self-reported noise cannot be ignored. The perceived noise levels can vary depending on individuals. Thus, the self-reported noise might not always assess the actual noise exposure which could cause systematic overestimation of noise exposure levels. No other comorbid conditions were taken into consideration except IHD history which shares common behavioral risk factors with the outcomes.
Almost all the studies in occupational noise were done in developed countries. Hence, occupational noise and its association with CHD deaths, stroke deaths and AMI in developed and developing countries could not be compared. This study has not specifically analyzed for blue-collar and white-collar workers. Job exposure matrix was not used in this study. Exposure misclassification might occur due to missing information on noise exposure level or duration of exposure to noise that could affect the true noise outcome.

6.4 Implication of the study
This study has introduced a new exposure noise-years, that could be used as a noise exposure in the future research. The subjective noise exposures used in this study could be useful in the research where objective assessments of noise exposure is not possible or in the research which prefer subjective assessment of noise exposure. The consistent results of this study could be used to compare with other future research with similar exposures and outcomes. The consistent results with no association in this study gives us insight to explore other factors that might cause CHD deaths, stroke deaths or AMI in occupational settings. Apart from the study results, the exposure variables and covariates used in this study could be applied in future research for different CVD outcomes, CVD deaths under different study settings.
7. CONCLUSION

In conclusion, this study showed consistent results where no statistically significant associations were observed between noise exposure group with CHD deaths, stroke deaths and AMI. Likewise, no significant associations were found between noise-years with CHD deaths, stroke deaths and AMI. The results of this study could not be fully compared with previous literature due to insufficient studies in occupational noise with CHD deaths, stroke deaths and AMI. In addition, there were quite few literatures on occupational noise and CVD in developing countries. Hence, this study helps in fulfilling the gap in knowledge for the association between occupational noise with CHD deaths, stroke deaths and AMI. However, more research is suggested to further study this association and extend the research setting in all parts of the world.

The previous studies for occupational noise and CVD outcomes had mixed results. The consistent results of this study, showing no associations might imply that the methods used in measuring the association might be more reliable compared to the methods used in previous studies with inconsistent results. However, the circumstances of this study method might not be applicable for all the studies. Thus, more attention is needed to investigate association of occupational noise exposure with CHD deaths, stroke deaths and AMI in different settings to conclude even more reliable results.
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