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Risk of ischemic heart disease among welders: a systematic review with meta-analysis.

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Indhold

1 Dansk resumé

Iskæmisk hjertesygdom (IHS) er hjertesygdom som følge af atherosklerose (åreforkalkning) i hjertets kranspulsårer. Akut myokardieinfarkt (AMI, blodprop i hjertets kranspulsårer) er en hyppig manifestation af IHS, som er den hyppigste dødsårsag i den vestlige verden. Der har længe været bred videnskabelig enighed om, at luftforurening i byerne kan øge risikoen for IHS blandt ældre og sygdomssvækkede personer. I forhold til den meget omfattende viden om udendørs luftforurening og IHS er det påfaldende så lidt man ved om risikoen for IHS blandt svejsere, der er udsat for op til 100 gange højere eksponeringsniveauer for partikler og gasser end bybefolkninger.

Formål: Formålet med denne rapport er

1) at beskrive og evaluere den videnskabelige litteratur vedrørende sammenhængen mellem erhvervsmæssig eksponering for svejserøg og risiko for IHS.
2) at undersøge, om risiko for IHS påvirkes af særlige eksponeringskarakteristika ved svejsning såsom svejsemateriale, svejsemetode samt eksponeringens samlede varighed
3) at evaluere de mulige biologiske mekanismer på basis af videnskabelige studier om ændringer i biomarkører for hjertesygdom ved eksponering for svejserøg.

Definition af svejsning: Metal svejsning er en fremstillingsmetode, hvorved jern og metal sammenføjes ved smeltning af overfladerne. Svejseprocessen genererer dampe og gasser afhængigt af svejsemetode og typen af metal der svejses på. Koncentrationen af svejserøg som svejsere er udsat for afhænger udover af svejsemetode og materiale, af varigheden af svejsning (timer pr dag), generel og lokal udsugning, plads og beskyttelses udstyr. Forurening af arbejdsmiljøet kan ske hurtigt i mangel af god ventilation og ved svejsning i lukkede rum. Ifølge en stor serie feltmålinger var den gennemsnitlige eksponering for svejserøgspartikler i midten af firserne 1,1 mg/m^3 for TIG-svejsning, 3,0 mg/m^3 for MAG-svejsning og 3,5 mg/m^3 for MMA svejsning. Begrænsede data indikerer, at eksponeringsniveauerne ikke har ændret sig meget i løbet af de sidste årtier. Det anslås, at omkring 70.000 erhvervsaktive danskere udfører svejseopgaver, men der findes ingen data vedrørende fuldtidsbeskæftigede svejsere i modsætning til arbejdere der engang imellem udfører svejseopgaver. Der findes ligeledes heller ikke oplysninger om hvor mange der svejser i rustfrit stål og andre metaller, såsom aluminium.

Definition af IHS og potentiel mekanisme: IHS er en sygdom som er karakteriseret ved manglende blodforsyning og reduceret ilt tilførsel til hjertemuskulaturen som følge af åreforkalkning i hjertets kranspulsårer. Åreforkalkning er en kronisk inflammatorisk sygdom, der opstår ved fortykkelse af

pulsårenes inderste cellelag (intima). Det er foreslået at ultrafine partikler, der opstår i forbindelse med svejsning, kan trænge dybt ned i luftvejene og de yderste lungeafsnit og skabe en inflammatorisk tilstand, som kan medføre ændringer i blodets fibrinogen-indhold og koagulationsevne. Dette kan medføre øget risiko for blodpropper.

Andre har foreslået, at partikeleksponering kan føre til ændringer i det autonome nervesystem. Forstyrrelser i hjertets autonome nervesystem kan måles ved hjertefrekvens (HR), variabilitet i hjertefrekvens (HRV) og blodtryk, som styres af en balance mellem det sympatiske og parasympatiske nervesystem. Nedsat HRV er associeret med øget risiko for kardiovaskulær morbiditet og mortalitet blandt udsatte grupper, og der er evidens for faldende HRV i relation til øget partikeleksponering. Det er også foreslået, at ændringer i det autonome tone kan indlede hjertearytmier eller bidrage til ustabilitet af vaskulære plaques (åreforkalknings propper).

Forekomst: Omkring 420.000 danskere lever med kardiovaskulær sygdom, hvoraf 150.000 skyldes IHS. Selv om prognosen for hjertekarsygdomme er forbedret betydeligt de seneste år, er omkring 10.500 årlige dødsfald forårsaget af hjerte relaterede sygdomme og 6.300 af disse skyldes IHS.

METODE

Litteratursøgning: Gennem en systematisk litteratursøgning i PubMed og EMBASE har vi identificeret epidemiologiske studier omhandlende eksponering for svejserøg og risiko for IHS publiceret i perioden 1979 til 2010. Alle studier der havde et kvantitativt mål for risiko for IHS ved svejsning blev inkluderet uanset design og kvalitet. Søgningen omfatter både mortalitets- og morbiditetsstudier og der blev udfoldet store anstrengelser for at identificere relevante data fra især mortalitetsstudier, som ikke eksplicit var designet med henblik på undersøgelse af sammenhæng mellem svejsning og iskæmisk hjertesygdom.

Definition af eksponering: Eksponering blev defineret som svejsearbejde eller erhvervsmæssig udsættelse for svejserøg. På grund af den begrænsede mængde af epidemiologiske undersøgelser vedrørende svejsning og IHS, var det ikke muligt at præcisere eksponeringen yderligere.

Definition af udfald: Udfaldet blev defineret som IHS i form af akut myokardieinfarkt og andre iskæmiske hjertesygdomme (ICD8, 410-414, ICD9, 410-414, ICD10, I20-I25), men på grund af et lille antal videnskabelige undersøgelser af sammenhængen mellem svejsning og IHS (n=12), valgte vi at inkludere den mere uspecifikke diagnose kardiovaskulær sygdom, hvis oplysninger om den præcise diagnose IHS manglede.

Kvalitetsvurdering: Kvaliteten af de videnskabelige studier blev vurderet individuelt af to forfattere i henhold til otte punkter vedrørende rapporteringens udførlighed (beskrivelse af studiepopulation, studie design, data indsamlings procedure, responsrate, inklusions- og eksklusions kriterier, definition af eksponering og udfald). Herudover vurderedes separat bias (selektions- og recall bias og healthy worker effect) og konfounding (køn, alder, rygning og socioøkonomisk status). Eventuelle uoverensstemmelse mellem forfatternes vurderinger blev løst ved konsensus.

Data analyse: I ni af de atten undersøgelser der indgår i denne rapport var der sammenlignelige mål for risikoen for IHS. Vi kunne derfor på basis af disse studier beregne en gennemsnitlig risiko med en metodik, hvor det enkelte studies indflydelse på gennemsnittet er vægtet i forhold til studiets størrelse. Store studier med mange deltagere blev tillagt større vægt end små studier med få deltagere. I særskilte analyser så vi på den vægtede gennemsnitlige risiko for IHS i studier der anvendte intern frem for ekstern referencegruppe. En intern reference gruppe er oftest metal arbejdere der ikke svejser og derfor mere sammenlignelig med svejsere end udtræk af den almindelige befolkning, der er anvendt i andre studier (ekstern reference). I særskilte analyser så vi endvidere på undersøgelser af akut myokardieinfarkt (blodprop ved hjertet), som er mere veldefineret end andre former for IHS og kredsløbssygdomme i almindelighed. Endelig foretog vi analyser for at afdække om små studier i højere grad end store studier viste en positiv sammenhæng mellem svejsning og IHS (røgfanegrafer). Sidstnævnte kan skyldes såkaldt publikationsbias, som anses for en væsentlig årsag til fejlagtige resultater i meta-analyser.

RESULTATER

Den systematiske litteratursøgning resulterede i 18 kohorte studier med risiko estimater for IHS (12 studier) og uspecificeret kardiovaskulær sygdom (6 studier). Seksten studier var mortalitetsstudier og to var morbiditetsstudier. Udfaldet blev ientificeret gennem dødsattester, hospitalsindlæggelser og spørgeskemabesvarelser. Den samlede studiepopulation på baggrund af de 18 studier bestod af 66.998 individer og de fleste undersøgelser var fra de skandinaviske lande.

Elleve af de 18 studier rapporterede en øget risiko for IHS og/eller kardiovaskulær sygdom blandt svejsere, men kun seks af disse fandt en signifikant sammenhæng. Et studie fandt en signifikant reduceret risiko for kredsløbssygdomme. I meta-analysen baseret på 9 studier (10 estimater) med sammenlignelige data fandt vi en let øget risiko for IHS på 9% (95% CI; 1,00, 1,19). I en analyse stratificeret på om der var anvendt intern (oftest fra samme eller tilsvarende virksomheder) eller ekstern reference gruppe (oftest baggrundsbefolkningen), fandt vi en meta-RR på 1,39 (95% CI; 0,96, 2,02) for x studier baseret på intern reference gruppe. Meta-RR var 1,08 (95% CI; 0,99; 1,18) for studier baseret på ekstern reference gruppe. I analysen af de specifikke udfald, AMI og andre IHS, var

risikoen for AMI øget væsentlig (RR = 1.69, 95% CI; 1,18, 2,42), analysen var dog kun baseret på 3 studier. Vi observerede ingen sammenhæng med andre IHS.

DISKUSSION

I den samlede meta-analyse, fandt vi en let øget risiko for IHS blandt svejsere. Ved analysen stratificeret på referencegruppe, fandt vi en risiko på omkring 40% blandt de undersøgelser, som brugte en intern referencegruppe. Risikoen for AMI var omkring 70% i den stratificerede analyse på udfald (AMI og andre IHS). To af de tre undersøgelser vedrørende risikoen for AMI var undersøgelser af sygelighed, som er mere følsomme end mortalitetsstudier, fordi sidstnævnte repræsenterer en blanding af prognostiske og ætiologiske faktorer. En anden forklaring kan være, at der ved AMI diagnosen er mindre risiko for misklassifikation end ved andre IHS, som kan omfatte en mere heterogen gruppe af sygdomme.

De tilgængelige studier har flere begrænsninger, 1) antallet af undersøgelser er få og meget få er designet til primært at undersøge sammenhængen mellem svejsning og IHS, 2) derfor var det heller ikke muligt at undersøge eksponering-respons sammenhængen, timing mellem eksponering og udfald eller sårbare subgrupper, 3) størstedelen af undersøgelserne var baseret på utilstrækkelige data, hvor kontrol af potentielle konfoundere, såsom rygning, ikke var mulig, 4) og den relativt beskedne risikoforøgelse kan være et resultat af (residual)-confounding.

Vi har også identificeret 9 undersøgelser vedrørende svejsning og biologiske markører for IHS i blod, hvor der er nogle holdepunkter for at udsættelse for svejserøg i løbet af en arbejdsdag kan føre til ændringer i hjertefunktionen og i koncentrationen af inflammationsmarkører i blodet. Om dette har betydning for risiko for IHS og anden hjertesygdom på længere sigt er dog usikker.

KONKLUSION

Der er fundet nogle holdepunkter for en moderat øget forekomst af iskæmisk hjertesygdom ved svejsearbejde men det tilgængelige datamateriale er utilstrækkeligt og for heterogent til at drage pålidelige konklusioner vedrørende kausalitet.

EVALUAERING

Den epidemiologiske evidens er baseret på en systematisk gennemgang af litteraturen og meta-analyse, der præsenteres i denne rapport. Evidensen er bedømt i henhold til de kriterier, som Dansk Selskab for Arbejds- og Miljømedicin har opstillet.

Hypotese	Udsagn	Vurdering i forhold til DASAM kriterier
1	Eksponering for svejserøg øger risikoen for udvikling af IHS	+ (begrænset evidens)
2	Risikoen for IHS blandt svejsere er afhængig af eksponeringskarakteristika, herunder type af materiale der svejses på, svejsemetode og eksponerings varighed.	0 (utilstrækklig evidens)
3	Eksponering for svejserøg inducerer ændringer I biomarkører for IHS	+ (begrænset evidens)

Hypotese 1: Få epidemiologiske studier viser en beskeden øget risiko for IHS blandt svejsere men det kan ikke afgøres med rimelig sikkerhed om dette kan tilskrives tilfældighder, bias og/eller confounding.

Hypotese 2: På baggrund af tilgængelige data er det ikke muligt at vurdere om risiko for IHS er afhængig af eksponeringskarakteristika.

Hypotese 3: Få eksperimentelle studier af god kvalitet har rapporteret højere niveauer af visse biomarkører for inflammation og nedsat *heart-rate-variability* (HRV). Mekanismerne er ikke afklarede og betydningen for mulig forekomst af IHS er usikker.

2 English summary

Worldwide ischemic heart disease (IHD) is the leading cause of death. There has long been broad scientific consensus that air pollution in major urban cities is associated with a modest increased risk of IHD among the elderly and ailing people. In relation to the very broad knowledge about environmental particulate exposure in the cities and the risk of IHD, little is known about the risk of IHD among welders, that are exposed up to 100 times higher exposure levels of particles and gasses that arise from industrial welding.

Objective: The objective of this report commissioned by The Danish Working Environment Fund is

1) to describe and discuss the scientific evidence on causal links between occupational exposure to welding fumes and the risk of developing IHD.
2) to investigate whether the risk of IHD is affected by the characteristics of the exposure
3) to evaluate the possible biological mechanisms based on studies of changes in biomarkers of heart disease by welding exposure.

Definition of welding: Metal welding is a manufacturing method for joining pieces of metals together by melting the parts and using a filler to form a joint. The welding process generates fumes and gases, depending on what type of welding method and type of metal is used. The concentration of the welding fumes the welders are exposed to is, besides welding methods and material, dependent on welding intermittence (duration of welding, hours per day), general and local exhaust ventilation, space, and protection heltmet. Contamination of the environment can occur quickly in absence of good ventilation and with welding in confined spaces. The Danish Welding Institute found that the average exposure to welding fume particulate was 1,1 mg/m^3 for TIG welding, 3,0 mg/m^3 for MAG welding and 3,5 mg/m^3 for MMA welding. The exposure levels may not have changed much during the last decades. It is estimated that about 70.000 Danish workers are performing welding tasks on a regularly basis, but no data are available regarding full-time welders as opposed to workers performing welding tasks now and then or regarding stainless steel welding and welding in other metals/alloys as aluminum as opposed to mild steel.

Definition of IHD and mechanism: IHD is a disorder characterized by lack of blood supply and thereby reduced supply of oxygen to the heart muscle causing ischemia of the heart. This is often due to atherosclerosis in the coronary artery supplying the heart muscle. Atherosclerosis is a chronic inflammatory disease that arises from thickening of the arterial intima, the innermost layer of the artery. Exposure to welding fumes is suspected to result in adverse cardiac events as the particles from the welding processes are small and can penetrate deep into the airways and the lungs and cre-

ate pulmonary inflammation which can increase the coaguability of the blood and elicit cardiovascular events. Another mechanism by which air particulates may lead to adverse cardiac outcomes is by adverse effects on cardiac autonomic control. Disturbances in the cardiac autonomic nervous system are measured by biomarkers like heart rate variability (HRV), resting heart rate (HR) and blood pressure, which are modulated by a balance between the sympathetic and parasympathetic nervous systems. Decreased HRV predicts an increased risk of cardiovascular morbidity and mortality among vulnerable individuals, and there is evidence for decreasing HRV in relation to increasing PM exposure. The mechanisms responsible for this association are unclear, however it is suggested that alterations in the autonomic tone might initiate cardiac arrhythmias or contribute to the instability of vascular plaque.

Occurrence: In Denmark, the prevalence of cardiovascular diseases is around 420.000 and of which 150.000 is caused by IHD. Although the prognosis of cardiovascular disease has improved greatly, about 10.500 deaths per year are caused by heart related diseases and 6.300 of these are due to IHD in Denmark.

METHODS

Literature search: This report is based upon the public scientific literature and no original data is included. Through literature searches in PubMed and EMBASE we identified papers addressing welding exposure and risk of IHD. We included original papers in English published 1979-2010 if they provided quantitative estimates of risk of cardiovascular morbidity or mortality in relation to occupational welding.

Exposure definition: The exposure of interest was welding work or exposure to welding fumes. Because of the limited amount of epidemiological studies with risk estimates for IHD, it was not possible to specify the type of welding exposure by metal fumes and gases.

Outcome definition: The outcome of interest was IHD in terms of AMI and other IHD (ICD-7, ICD8; 410-414, ICD9; 410-414, ICD10; I20-I25), but due to a small number of scientific studies investigating the association between welding and IHD (n=12), we chose to expand the outcome including unspecific diagnoses as circulatory and heart diseases if there was no information on a specific diagnosis.

Quality assessment: Two of the authors independently assessed the inclusion criteria for each paper and disagreements were resolved by consensus. The scientific quality of the studies was rated according to completeness of reporting of eight essential study characteristics (population character-

istics, study design, sampling procedure, inclusion and exclusion criteria, response rate, exposure ascertainment and outcome ascertainment) and the potential for bias and confounding.

Data analyses: We computed the average risk across studies in random effects meta-analysis in which the contribution of each study was weighted by the inverse variance. We computed a common risk estimate across all 9 studies that were eligible for meta-analysis explicitly addressing IHD as outcome. Sub-analyses were stratified according to type of reference group (internal or external) and on type of IHD, AMI and other IHD. To check for publication bias we produced funnel plots of the standard error by the logarithm of the relative risk.

RESULTS

We identified 18 follow-up studies that provided risk estimates for IHD (12 studies) or unspecified cardiovascular disease (6 studies). Two studies addressed IHD morbidity and 16 were mortality studies and the outcome of interest was identified mostly through death certificates, hospitalization registries and self-reports. These studies addressed in total 66.998 persons and the majority of the studies were conducted in Scandinavia.

Eleven studies reported an increased risk for IHD and CD among workers exposed to welding fumes, however of these only six found a significant association and one found a significantly reduced risk for diseases of the circulatory system. In our random effect meta-analysis, we found an overall borderline significant increased risk of IHD of 9% (95% CI; 1.00, 1.19). The analysis was based on 10 risk estimates from 9 studies. In the stratified analysis by internal and external reference group we found an RR of 1.39 (95% CI; 0.96, 2.02). The RR was 1.08 (95% CI; 0.99; 1.18) for the external reference analysis. In the analyses of the specific outcome, we estimated an increased significant risk of 69% (95% CI; 1.18, 2.42) of AMI (based on 3 studies), but found no association with other IHD.

DISCUSSION

In the overall meta-analysis, we found a small borderline significant risk of IHD among welders. When stratifying the analysis by reference group, the risk was of some 40% among studies that used an internal reference group. The risk of AMI was of some 70% in the analysis stratified by outcome (AMI and other IHDs) and the risk for other IHDs was not increased. These findings may be explained by the fact that two of the three studies addressing the risk of AMI were studies of morbidity, which are more sensitive than mortality studies because the latter represents a mixture of prognostic and etiologic factors. Another explanation may be that AMI diagnosis is less prone to misclassification than other IHDs which may include a more heterogeneous group of diseases.

The available data have several limitations; 1) the number of studies are few and very few were specifically designed to examine the association between welding and IHD, 2) because of the latter, it was not possible to investigate the exposure-response relation, timing between exposure and outcome or susceptible subgroups, 3) the majority of studies were based on inadequate data, where controlling for potential confounding factors, such as smoking, was not possible, 4) and the small magnitude of risk elevation in our mate-analysis raises concern for biased results.

We also identified 9 studies concerning welding exposure and biological markers for IHD in blood. The literature indicates that there is a link between exposure to welding fumes and changes in biomarkers of CVD and IHD. The mechanisms are not clearly understood, but the studies report that welding fumes induce changes in heart function and in inflammatory markers in blood. Even though the scientific evidence suggests that exposure to welding fumes induces changes in biomarkers of heart function, it is of importance to be aware of the problematic interpretation of these changes in relation to the long term effects.

CONCLUSION

There is a strong heterogeneity in estimates of risk for IHD according to occupational metal welding across a limited number of observational studies. Overall available data is too limited to draw reliable conclusions as to possible risk of IHD in relation to metal welding. There is a need to perform follow-up studies of morbidity among a cohort of welders with appropriate external reference groups to fully investigate whether welders are at higher risk for IHD. Studies concerning the biological mechanisms by changes in biomarkers of IHD indicate that exposure to welding fumes can induce systemic inflammation and increase HRV, although the mechanisms are not fully understood and should be carefully interpreted.

EVALUATION

The epidemiological evidence is based upon the systematic review and meta-analysis presented in this report and rated according to the criteria defined by The Danish Society of Occupational and Environmental Health (Appendix 1).

Hypothesis	Issue	Rating according to DASAM criteria
1	The exposure to welding fumes is causally linked to development of ischemic heart disease.	+ (limited evidence)
2	The risk for ischemic heart disease among welders is dependent on the characteristics of the exposure, e.g. material welded, welding method and the length of exposure.	0 (insufficient evidence)
3	Exposure to welding fumes induces changes in biomarkers of heart disease.	+ (limited evidence)

Comments:

Hypothesis 1: Few epidemiological studies indicate a modest elevated risk of IHD among welders but chance, bias and confounding cannot be ruled out with reasonable confidence and results are not corroborated by other studies.

Hypothesis 2: Available data are insufficient to determine if specific welding process are imposing a higher risk than others.

Hypothesis 3: Few experimental studies have reported higher levels of some biomarkers of inflammation in blood and increased HRV. The evidence indicates that exposure to welding fumes has effects on biomarkers for IHD, although it is unknown whether the effects have a negative impact on the health of the welders and in addition, the mechanisms are not clearly understood.

3 Foreword

Following an international open call issued by the Danish Work Environment Fund in August 2012 with application deadline in September 2012, the authors received a research grant, which financed the present project. The report was prepared from February 1 through September 30 by the following working group at the Department of Occupational and Environmental Medicine, Bispebjerg Hospital and University of Copenhagen:

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A draft report was submitted by August 19 to professor Kjell Torén, Section of Occupation and Environmental Medicine, University of Gothenburg, Sweden and professor Christian Tobias Torp-Pedersen, Department of Health Science and Technology, Aalborg University, Denmark, who performed independent reviews of the report. The report is entirely the responsibility of the working group and does not necessarily express the views of the external reviewers or the funding agency.

Bispebjerg October 01 2013,
The authors

4 Introduction

Occupational exposure to welding fumes and risk of adverse health outcomes has been described in numerous scientific studies during the past three decades. The majority of studies address the risk of reduced lung function and cancer. Even though welding is one of the main crafts in construction work and workers may be exposed to high concentrations of small and possibly toxic metal particulates, few have investigated the effect of welding on the risk for ischemic heart disease (IHD). On the contrary, there has long been broad scientific consensus that air pollution in major urban cities is associated with a modest increased risk of IHD among the elderly and ailing people (1). A series of longitudinal studies have found a close day-to-day association between levels of air pollution and hospitalization and death due to IHD. The importance of the duration of exposure and disease mechanism remains unresolved. However, it is a widespread assumption that ultrafine particles can cause an inflammation of the airways which can affect blood composition and pose a risk of thrombosis (2-4). In relation to the very broad knowledge about environmental particulate exposure in the cities and the risk of IHD, it is striking how little is known about the risk of IHD among welders, that are exposed to 10-100 times higher exposure levels of particles and gasses that arise from industrial welding (5).

5 Objectives

The objective of this review is

- to systematically evaluate the scientific evidence on causal links between occupational exposure to welding fumes and the risk of developing ischemic heart disease.
- to investigate whether the risk for ischemic heart disease is affected by the characteristics of the exposure, namely material welded (mild steel, stainless steel), welding method (MMA manual metal arc welding, TIG tungsten inert gas welding, MAG metal active gas welding) and the duration of exposure.
- to evaluate the possible biological mechanisms based on studies of changes in biomarkers of ischemic heart disease by welding exposure.

6 General state of the art

6.1 Definition of welding

Metal welding is a manufacturing method for joining pieces of metals together by melting the parts and using a filler to form a joint. The welding process generates fumes and gases, depending on what type of welding method and type of metal is used. The chemical properties of welding fumes can be quite complex and most welding materials are a mix of diverse steels such as iron, chromium, nickel, manganese, silica and others. The evaporation of these alloying elements depends also on the concentration in the steel, e.g. the fumes from mild steel welding contain more than 80% of iron and fumes from stainless steel welding often contain about 20% chromium with 10% nickel (6). There are more than 80 different types of welding, but the most common types are shielded manual metal arc welding (MMA) gas metal arc welding (GMA), flux-cored arc welding (FCA), mild steel metal active gas (MAG), tungsten intert gas welding (TIG) and gas tungsten arc welding (GTA). Each welding method has its own technological advantages but the health hazards may differ by varying levels of exposure and chemical composition of the welding fume particulates and gases (6), a fact that is demonstrated by the welding process specific Danish threshold limit values (7).

6.1.1 Occupational threshold limit values

The Danish occupational threshold limit values (TLVs) for welding dust concentration in ambient air are based on the welding method and the welded material. In general welding of nickel-chromium alloys are considered a greater hazard than welding of mild steel because of the high content of chromium and nickel. Furthermore, MMA stainless steel welding is considered more hazardous than TIG stainless steel welding because chromium in MMA welding mostly occur as water-soluble hexavalent chromium while TIG welding mostly emits elemental and water-insoluble trivalent chromium (8). Hexavalent chromium and some nickel species are experimental carcinogens and chromates are by IARC classified in group 1 (human carcinogen with high level of evidence) (9). As stated in Table 1, the TLV for MMA welding of stainless steel is 0,5 mg/m^3 and for TIG of stainless steel it is 1,1 mg/m^3. In general the occupational exposure limit values are updated regularly as new knowledge becomes available but the Danish process specific welding TLVs have remained unchanged for at least 20 years. The limits are set nationally, meaning that the limits in other countries can be different from the Danish TLVs presented in this report.

6.1.2 Contamination of the welding environment

The concentration of the welding fumes in ambient air at the workplace is, besides welding methods and material, dependent on welding intermittence (duration of welding, hours per day), general and

local exhaust ventilation and space. Contamination of the environment can occur quickly in absence of good ventilation and with welding in confined spaces. The Danish Welding Institute performed 44 full shift measurements of the particulates in the breathing air in randomly selected welders in 1987 and they found that the average exposure to welding fume particulate was 1,1 mg/m^3 for TIG welding, 3,0 mg/m^3 for MAG welding and 3,5 mg/m^3 for MMA welding (10). To our knowledge there are no recently performed official measurements of the particulate levels in the breathing air among welders, but a new series of measurements based upon air sampling on filters in the breathing zone of randomly selected welders in 2008 found company and welding process specific levels close to welding fume measurements in 1987 (10). Although monitoring of welding exposure at Danish workplaces have been neglected, the limited available data thus indicate that exposure levels may not have changed much during the last decade. However, the welders are a heterogeneous group with work duties in different settings and conditions: outdoors, underwater, above ground on construction sites and indoors in open or confined spaces. For determination of the health effects of welding, the actual concentration of welding particulates delivered to the lung is more important than the ambient pollution. Dependent on the general working conditions, such as local ventilation and eye protection helmet, the fume concentrations in the breathing zone inside the helmet may be significantly lower than outside the helmet (6). Therefore the welders may not be exposed to the same concentration of welding particulates even though they are welding the same type of steel and using the same welding method. Besides dangerous fumes and gases, the welders are also exposed to heat, noise, uncomfortable postures involved in the work, vibration, radiation and many other (Table 2) (6).

Table 1. The Danish threshold limits for welding methods and materials			
Material	**Method**	**Coating**	**Process dependent limit (mg/m^3)**
Normal construction iron	MMA (Manual Metal Arc)	Ironoxide and zinc-primers or no coating	1.7
	MIG/MAG (Metal Inactive/Active GAS)	-	1.6
	Oxygen	-	1.7
Stainless and acid restistant steel	MMA (Manual metal Arc)		0.5
	TIG (Tungsten Intert Gas)		1.1

Source: Arbejdstilsynet, AT-vejledning, Stoffer og materialer, 2007(7)

6.1.3 Prevalence of welders

It is estimated that about 70.000 Danish workers are performing welding tasks on a regularly basis (11), but no data are available regarding full-time welders as opposed to workers performing welding tasks now and then or regarding stainless steel welding and welding in other metals/alloys as aluminum as opposed to mild steel.

Table 2. Hazardous byproducts of welding

Fume	Gases	Radiant Energy	Other Hazards
Aluminium	Carbon Dioxide	Ultraviolet	Heat
Cadmium	Carbon Monoxide	Visible	Noise
Chromium	Nitrogen Oxide	Infrared	Vibration
Copper	Nitrogen Dioxide		
Fluorides	Ozone		
Iron			
Lead			
Manganese			
Mangnesium			
Molybdenum			
Nickel			
Silica			
Titanium			
Zinc			

Source: Antonini, 2003 (6)

6.2 Ischemic heart disease

Worldwide IHD is the leading cause of death. IHD is a disorder characterized by lack of blood supply and thereby reduced supply of oxygen to the heart muscle causing ischemia of the heart. This is often due to atherosclerosis in the coronary artery supplying the heart muscle (12). Atherosclerosis is a chronic inflammatory disease that arises from thickening of the arterial intima, the innermost layer of the artery (13). This thickening is a result of the accumulation of fatty materials such as fat, cholesterol and calcium which creates plaque. With time the plaque hardens and grows, and narrows the lumen which thereby limits the flow of oxygen rich blood. Acute myocardial infarction (AMI) occurs when the atherosclerotic lesion ruptures and causes stenosis of the artery supplying the heart muscle (14).

6.2.1 Clinical manifestations of ischemic heart disease

AMI is the most important clinical manifestation of IHD which may cause immediate death because of cardiac arrest, complete recovery or recovery with permanently weakened heart muscle associated with signs of heart disease (weakness, breathing difficulties and oedema of the lower extremities). Other manifestations of coronary atherosclerosis are uncompensated heart disease developing slowly without preceding AMI and disruption of the electrical system causing cardiac arythmia (15).

6.2.2 Incidence

In Denmark, the prevalence of cardiovascular diseases is around 420.000 and of which 150.000 is caused by IHD. Of those who suffer from IHD about 72.000 have had an AMI (16). The incidence of IHD is age dependent as presented in Figure 1 (17). Among first-time hospitalized patients and those who died due to IHD was the incidence about 25.000 in 1990 in Denmark (18). For comparison the incidence was 21.300 in 2008, which reflects a decrease of about 15%. The authors of a recent Danish report on heart statistics expect that the incidence of IHD in 2025 will be 30% lower compared with the level in 1990 (18).

6.2.3 Mortality due to IHD and prognosis

Although the prognosis of cardiovascular disease has improved greatly, about 10.500 deaths per year are caused by heart related diseases and 6.300 of these are due to IHD in Denmark. The mortality rates are higher among men than women, though the mortality has decreased by more than 50% in both sexes since 1960 (18) (Figure 2). The decrease in mortality is believed to be caused by a combination of modern cardiological treatments (40%) and reduction in major risk factors (60%), primarily smoking (19). Figure 3 illustrates the age-standardized proportional contribution of specific

treatments and risk factor changes to coronary heart disease mortality reduction in England and Wales (19).

The improved prognosis for patients with IHD is especially seen in patients with AMI. A Danish analysis of first-time patients with AMI in 2000 showed that about 25% died before hospitalization, further 20% deceased within one year after hospital admission, and 55% survived the first year after hospitalization. In comparison, 42% survived the first year after hospital admission in 1989 (20). The mortality is strongly associated with age where the mortality is 35% higher among the highest age group (85+ years) compared with 65-74 years. However, the decrease in mortality due to AMI is observed in all age groups. Figure 3 illustrates the age-standardized mortality curves within 28 days after hospital admission among men and women from 1985 to 2002. As can be seen, the mortality had decreased for both sexes for more than 50% in 17 years (Figure 4) (20).

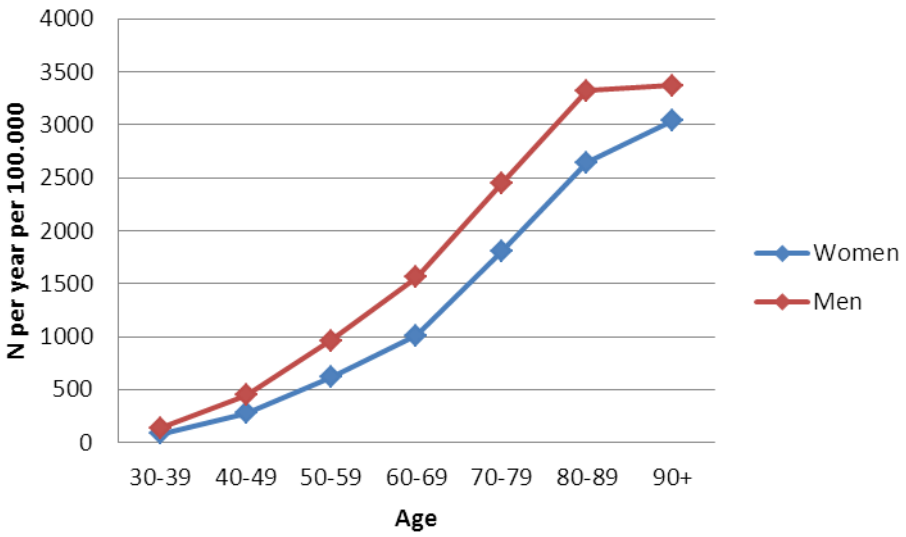

***Figure 1**. Age dependent incidence of IHD among men and women without prior disease. Data from Statens Institut for Folkesundhed (17).*

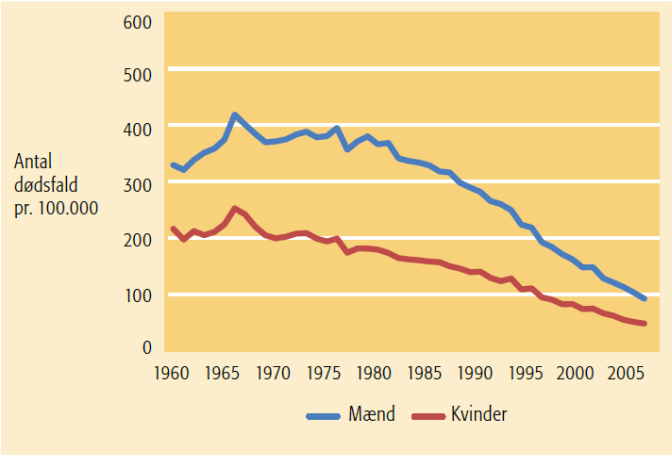

Figure 2. *Age-standardized mortality by IHD in Denmark from 1960 to 2008 among men and women. The blue curve presents men and the red women. Source: Data from OECD, Dansk Hjertestatistik (18)*

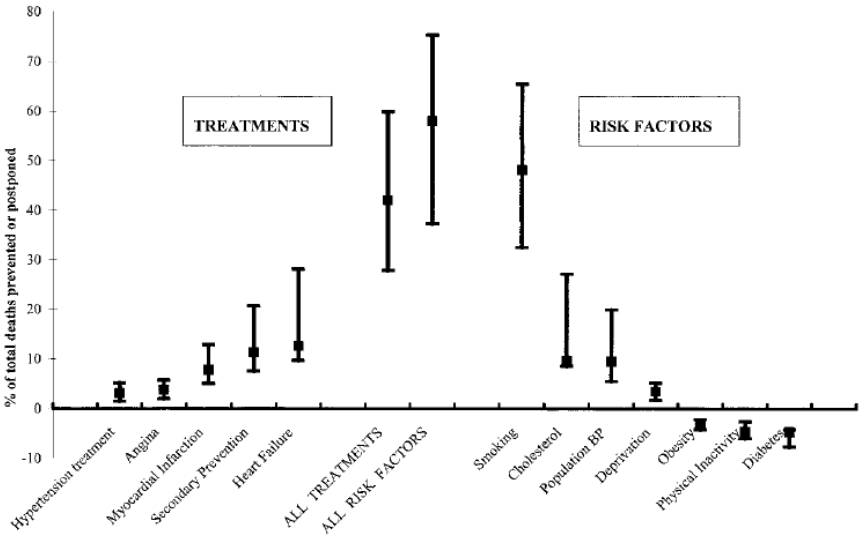

Figure 3. *Proportional contributions of specific treatments and risk factor changes to coronary heart disease mortality reduction in England and Wales, 1981 to 2000. Source: Unal et al. 2009 (19)*

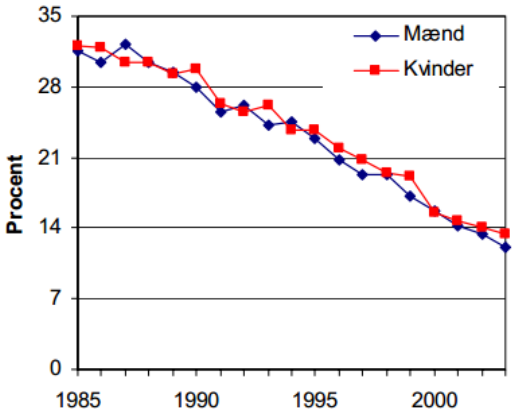

Figure 4. *Mortality within 28 days after hospital admission among first-time patients with AMI in the period 1985 to 2002. The blue line presents men and the red women.*
Source: Sundhedsstyrelsen, 2005 (20)

6.2.4 Risk factors for ischemic heart disease

Several factors are thought to increase the risk of developing IHD. The risk factors can be classified into genetic, biological and lifestyle factors. Among the genetic and biological risk factors, the most important are hypertension and hypercholesterolemia. However, age, diabetes and family history of IHD are also factors that increase the risk for development of IHD (17;21-24).

Moreover, IHD is related to lifestyle factors such as abdominal obesity, irregular or lack of physical activity and smoking. It is believed that moderate overweight (body mass index, BMI, between 25 and 30kg/m^2) and obesity (BMI above 30kg/m^2) are associated with respectively 32% and 81% increased risk for coronary heart disease when compared with normal weight (BMI=18-25 kg/m^2) (24). When adjusted for blood pressure and cholesterol, the risk decreases to 17% for moderate overweight and 49% for obesity (24). A series of different risk factors can increase the risk for IHD solely but also in combination with each other. High blood pressure is strongly associated with overweight and physical inactivity but it can solely increase the risk for IHD without the other factors being present (19). High serum levels of cholesterol are causally related to an increased risk of IHD and the connection between serum cholesterol levels and future occurrence of IHD is continuous and positive throughout the range of cholesterol levels (22). By lowering the levels of serum cholesterol with diet or drugs the incidence of IHD decreases (22).

The most important lifestyle risk factor for IHD is smoking. The risk for thrombosis doubles by smoking 3-6 cigarettes daily. Compared to non-smokers, men who smoke 20 cigarettes per day have 3 to 5

times increased risk for thrombosis. A marked decrease for IHD is observed among people who have quit smoking compared to those who continue smoking (25). A study from 2004 found that by reducing smoking, 48% of CHD related deaths could be prevented (Figure 2) (19).
Diabetes is also a known risk factor for IHD, since diabetics have an increased risk for artherosclerosis (26;27). Psychosocial stress may also be associated with increased risk of acute myocardial infraction, as a cohort study found that individuals who responded to be stressed at home and at work had an increased risk of IHD up to OR=2.36 (28), however the association with stress at work was not observed among women. Another study among predominantly female public service workers, could not lend support to the hypothesis that psychosocial workload increased the risk of IHD (29). Daily consumption of fruit and vegetables is estimated to have a protective effect, together with regular physical activity and moderate alcohol consumption (23).

6.3 Mechanism

Exposure to air pollution might result in adverse cardiac events by causing pulmonary inflammation that may give rise to a systemic inflammatory response (30). Arthrosclerosis is an inflammatory disease and studies have proven a clear association between the levels of inflammation and risk of cardiovascular disease (31). In studies of exposure to welding fumes it has been observed that the particles from the welding processes are small in the range of 0.01-0.10 μm and the majority are of submicron size with a diameter up to 0.8 μm (32;33). Due to their small size, they can penetrate deep into the airways and the lungs and create pulmonary inflammation with subsequent inflammatory response. Inflammatory cytokines are produced in the lungs and released into the blood circulation. As a result of this process, the coaguability of the blood may increase and elicit cardiovascular events (31).

Another mechanism by which air particulates may lead to adverse cardiac outcomes is by adverse effects on cardiac autonomic control. Disturbances in the cardiac autonomic nervous system are measured by biomarkers like heart rate variability (HRV), resting heart rate (HR) and blood pressure, which are modulated by a balance between the sympathetic and parasympathetic nervous systems. Decreased HRV predicts an increased risk of cardiovascular morbidity and mortality among vulnerable individuals, and there is evidence for decreasing HRV in relation to increasing PM exposure (34-36). The mechanisms responsible for this association are unclear, however it is suggested that alterations in the autonomic tone might initiate cardiac arrhythmias or contribute to the instability of vascular plaque (34).

Many steps along the paths of inflammation and coagulation are not fully understood, however the mechanisms of IHD are to some degree possible to identify through biomarkers. Biomarkers are of different variety, some are measured in a biosample, such as a blood, urine or tissue test, some are recordings obtained from a person, such as blood pressure and electrocardiogram (ECG), and others may be an imaging test, as echocardiogram or CT scan. Biomarkers can indicate, besides health and disease characteristics also the level and type of exposure to an environmental factor (37). The biomarkers for identification of IHD can be classified into three groups; those used for identification of *1) arterial vulnerability,* as functional markers (e.g. blood pressure, endothelial dysfunction and arterial stiffness), structural markers (e.g. coronary artery calcium, carotid intimal-medial thickness) and serological biomarkers (e.g. abnormal lipid profile, indicators of inflammation such as interleukin-5 (IL-6), IL-18 and C-reactive protein (CRP)), 2) *blood vulnerability*, as indicators of hypercoagubility (fibrinogen, D-dimer and increased von Willebrand Factor (vWF)), and 3) *myocardial vulnerability*, as structural markers (e.g. left ventricle hyperthropy (LVH), LV dysfunction), functional markers (e.g. exercise stress test/stress echo, positron emission tomography (PET), and serological markers such as troponins. The list of the specific biomarkers of IHD is long and only some key biomarkers are mentioned above.

7 Methods

This report is based upon the published scientific literature and no original data are included.

Literature search

We conducted two literature searches addressing morbidity and mortality, respectively. From Medline and EMBASE we retrieved peer-reviewed English-language publications between January 1966 and April 2013 (EMBASE from 1974) by combining medical subject headings and generic terms for the exposure and outcomes. Retrieved publications were limited to human studies and no effort was made to retrieve unpublished publications. In total we identified 18 original papers addressing the risk of cardiovascular disease (also IHD) in relation to welding.

Exposure definition

The exposure of interest is welding work or exposure to welding fumes. Because of the limited amount of epidemiological studies with risk estimates for IHD, it was not possible to specify the type of welding exposure by metal fumes and gases.

Outcome definition

The outcome of interest is IHD in terms of AMI and other IHD (ICD-7, ICD8; 410-414, ICD9; 410-414, ICD10; I20-I25), but due to a small number of scientific studies investigating the association between welding and IHD (n=12), we also included unspecified cardiovascular disease because in particular older studies do not distinguish between IHD and other types of heart disease.

Data extraction

Two of the authors (EM and PK) independently assessed ex- and inclusion criteria for each paper and extracted information according to a scheme with variables defined a priory. This included study population, study design, population size, response rate, age distribution, exposure and outcome ascertainment, risk estimates and confidence intervals. Disagreements during assessments of papers were resolved by consensus.

Completeness of reporting

The completeness of reporting of essential study characteristics was evaluated by two of the authors (EM and PK) and for each characteristic we assessed whether sufficient detail was provided (yes/no). These study characteristics included eight items: population characteristics, study design, sampling procedure, inclusion and exclusion criteria, response rate, exposure ascertainment and

outcome ascertainment. Giving each study characteristic an equal weight (1 point), we rated the completeness of reporting as adequate if the sum was six or more.

Statistical analysis

To obtain an overall estimate of the risk of IHD in relation to welding we computed the average risk across studies in random effects models in which the contribution of each study was weighted by the inverse variance (38). This meta-analysis was performed using STATA software (metan, metabias and funnel commands) (39).

First we computed a common risk estimate across all 9 studies explicitly addressing IHD as outcome. Second, we stratified the analysis according to type of reference group (internal or external). The internal reference group was defined as workers working within the same industry in similar jobs, who were not directly exposed to welding fumes. If the reference group is the background population or just matched on age and sex without having similar employment, then it was defined as external. Third, we stratified the analysis on type of IHD, AMI and other IHD. Fourth, to check whether smoking affects the association between exposure to welding fumes and IHD, we stratified the analysis on studies who have controlled for smoking and those who have not. To check for publication bias we produced funnel plots of the standard error by the logarithm of the relative risk.

8 Results

We identified 18 follow-up studies that provided risk estimates for IHD (12 studies) or unspecified cardiovascular disease (6 studies). Two studies addressed IHD morbidity and 16 were mortality studies and the outcome of interest was identified mostly through death certificates, hospitalization registries and self-reports. These studies addressed in total 66.998 persons and the majority of the studies were conducted in Scandinavia. Eleven studies reported an increased risk for IHD and CD among workers exposed to welding fumes, however of these only six found a significant association (40-45). Based on the few studies that assessed the risk of IHD among welders, we are unable to fully evaluate whether the risk of IHD is dependent on specific welding characteristics.

We included 9 studies with sufficiently homogeneous exposure and outcome information in a meta-analysis. Reasons for not being included in the meta-analysis were missing information on confidence intervals (43;46-50), one study investigated the risk of IHD only among stainless steel welders (51) and two studies had unspecified cardiovascular disease as outcome (52;53).

In our random effect meta-analysis, we found an overall borderline significant increased risk of IHD of 9% (95% CI; 1.00, 1.19). In the analysis stratified by smoking, we observed an increased but insignificant risk of 14% (95% CI 0.86, 1.53) among studies with adjustment for smoking. We also stratified our analyses according to the use of an internal or external comparison group. Three studies have used an internal reference group, five have used an external reference group and one study used both an internal and external reference group. Typically the external comparison groups were based on the general population rate of IHD. In the analysis of the studies using internal reference groups we found an RR of 1.39 (95% CI; 0.96, 2.02). The RR was 1.08 (95% CI; 0.99; 1.18) for the external reference analysis. In the analyses of the specific outcome, we estimated an increased significant risk of 69% (95% CI; 1.18, 2.42) of AMI (based on 3 studies), but found no association with other IHD (RR=6%; 95% CI 0.98, 1.14, based on 9 studies). In the analysis of possible publication bias, we found that there was no small-study effect (p=0.09).

8.1 Does exposure to welding fumes induce changes in biomarkers of heart disease?

We identified 9 studies investigating whether exposure to welding fumes is associated with changes in biomarkers of ischemic heart disease. These studies were controlled intervention studies with measures of lifestyle factors and biomarkers at baseline and assessments of fine particulates exposure and after-exposure biomarker status.

8.1.1 Cardiac autonomic function

A research group from Harvard School of Public Health has made a series of studies regarding fine particulate exposure and adverse effects on heart function, measured as HRV, inflammation, vascular function and circulating adhesion molecules (54-59). The group invited boilermakers from 1999 to 2006 at an apprentice welding school to participate in extensive ambulatory ECG monitoring over two 24-hour periods on a workday and a non-workday (exposure longer than 6 hours). In addition boilermaker welders were monitored for workday exposure to the fine fraction of particulate matter (PM) with a mass median aerodynamic diameter ≤2.5 μm ($PM_{2.5}$). $PM_{2.5}$ is considered to be especially toxic due to its ability to penetrate deep into the alveolar regions of the lung and cause adverse effects of the lung and heart related health, but also directly affect the cardiac autonomic function. The boilermaker welders were invited to participate in the study on multiple occasions, from which the research group has collected data to their investigations. The welders performed mostly shielded metal arc and TIG welding using mild steel and stainless steel. In the studies published by the research group, the welders were exposed to mean concentrations of $PM_{2.5}$ from 0.39 mg/m^3 (59) to 1.66 mg/m^3 (58) during the workday. The authors found that the workers experienced altered cardiac autonomic control with a 5 minute SDNN (standard deviation of the normal-to-normal intervals) decrease of 2.66% per 1 mg/m^3 increase in a 4-hour moving $PM_{2.5}$ average and HR increased by 1.02% (57). The 5-minute SDNN finding was corroborated by Fang et al. (2009), however greater declines in SDNN were observed among those with systemic inflammation and poorer vascular function (54). Cavallari et al. (2007) investigated the association between long-duration HRV and occupational exposure to $PM_{2.5}$ and observed a consistent inverse exposure-response relationship with decrease in all HRV measures with increasing $PM_{2.5}$ exposure. The decrease in HRV was most pronounced at night (56). Changes in vascular function among the welders were also observed after exposure to $PM_{2.5}$ as the afternoon augmentation index increased with 2.8% (55). The augmentation index can be used as a marker of cardiovascular risk (60).

8.1.2 Inflammation

The same research group found that $PM_{2.5}$ exposure was associated with a decrease in the soluble vascular cell adhesion molecule-1 (sVCAM-1), which is involved in leukocyte adhesion, and an increase in vWF antigen, a pro-coagulatory molecule. Both are markers of endothelial cell activation and function, because they are released by endothelial cells into the circulation upon interaction with inflammatory cytokines. An increase in sVCAM-1 and vWF is associated with future risk of adverse cardiovascular events and stroke (59). Kim et al. (2004) investigated the effect of exposure to welding fumes and $PM_{2.5}$ on acute systemic inflammatory response and observed that high levels of welding fume exposure is associated with an increase in WBC and neutrophil counts immediately after exposure in non-smokers. The same associations were not found in smokers, however, CRP levels

were increased in both smokers and non-smokers 16 hours after exposure. CRP levels were also associated with increasing levels of $PM_{2.5}$ both in smokers and non-smokers 16 hours after exposure, but the association with absolute neutrophil counts was only significant among non-smokers (58). Scharrer et al. (2007) measured 20 different biomarkers and found no significant association between HRV, hemostatic and acute inflammatory blood parameters and short-term exposure to welding fumes. vWF showed a trend towards increasing values, but it was not statistically significant. However, the study group of 20 volunteers was exposed to welding fumes of 3.5 mg/m^3 for only one hour (61). Bonzini et al (2009) observed that exposure to PM_1 (median exposure of 159 $\mu g/m^3$) and coarse PM (PM_{10}-PM_1 median exposure of 162 $\mu g/m^3$) were associated with increased systemic inflammation as measured as an increase in CRP, tissue-type plasminogen activator (t-PA) antigen, thrombin generation and shorter prothrombin time (PT) among 37 workers exposed for two workdays at a steel production plant (62). Ohlson et al. observed a 52% increase in IL-6 after the first day of working and a 17% increase in CRP after the second day in 73 persons working with welding, cutting, grinding and in foundries such as iron, aluminium, and concrete. The IL-6 values decreased after the second working day. These workers were exposed to a mean total dust exposure of 0.93 mg/m^3 for two workdays after their summer holiday (63).

9 Discussion

The systematic literature search yielded 18 epidemiological cohort studies that addressed the risk of IHD in relation to welding exposure. Because only two examined the risk of incident IHD, we chose to include mortality studies even though mortality is a less sensitive measure of IHD, because of the large and increasing survival rate for IHD morbidity. We included 9 studies in the meta-analysis.

9.1 Are welders at higher risk of IHD?

The epidemiological evidence of welder's risk of IHD is contradictory, some find an increased risk of IHD and others do not, however the majority of the results are insignificant. In the overall meta-analysis, we found a small borderline significant risk of IHD among welders. When stratifying the analysis by reference group, the risk was of some 40% among studies that used an internal reference group. When using an external reference group with the background population as reference, the true risk may be underestimated because of the healthy worker effect as healthy workers may be employed and the background population includes also the sick and disabled that are more likely to be unemployed.

The risk of AMI was of some 70% in the analysis stratified by outcome (AMI and other IHDs) and the risk for other IHDs was not increased. These findings may be explained by the fact that two of the three studies addressing the risk of AMI were studies of morbidity, which are more sensitive than mortality studies because the latter represents a mixture of prognostic and etiologic factors. Another explanation may be that AMI diagnosis is less prone to misclassification than other IHDs which may include a more heterogeneous group of diseases.

The available data have several limitations; 1) the number of studies are few and very few were specifically designed to examine the association between welding and IHD, 2) because of the latter, it was not possible to investigate the exposure-response relation, timing between exposure and outcome or susceptible subgroups, 3) the majority of studies were based on inadequate data, where controlling for potential confounding factors, such as smoking, was not possible, 4) and the small magnitude of risk elevation in our mate-analysis raises concern for biased results.

9.2 Does the risk of IHD among welders depend on the exposure characteristics?

All welders are to a varying degree exposed to airborne particulate matter emitted from the melt and welding electrodes. This includes exposures to particles in the ultrafine range that far exceeds numbers and concentrations encountered in environmental exposures from traffic-related air population. If the risk for IHD primarily is related to particle exposure we would not expect that the type of mate-

rial as mild steel, chromium-nickel alloys, aluminum and manganese enriches alloys would be an important determinant although the welding method is a strong determinant of fume concentrations. In any case, we are unable of making inferences regarding whether the risk of IHD depends on the characteristics of exposure on the basis of only three studies. The studies are of smaller sizes, however they indicate that there may be an increased risk depending on the length of exposure and concentration.

9.3 What could explain the increased risk of AMI?

We identified 9 studies concerning welding and biological markers for IHD in blood. The literature indicates that there is a link between exposure to welding fumes and changes in biomarkers of CVD and IHD. The mechanisms are not clearly understood, but the studies report that welding fumes, also measured as $PM_{2.5}$, induce changes in heart function (measured by SDNN, HRV and augmentation index) as well as in inflammatory markers in blood (measured as vWF, WBC, CRP, t-PA, thrombin generation, PT, and IL-6). Even though the individuals were exposed to varying concentrations of welding fumes for a short period of time compared to a lifelong occupational exposure, immediate effects in both heart function and biomarkers measured in blood were reported (54-59;62;63). However, the effect of the exposure was observed to be modified by smoking in one study (58), as an increase in WBC and neutrophil counts occurred among non-smokers only. Also poorer vascular function (measured as augmentation index and pulse pressure) and systemic inflammation (measured as CRP) appeared to aggravate the $PM_{2.5}$-related decline in HRV (54). Other factors, such as ABO phenotypes, may modify the association between exposure to welding fumes and risk of IHD, as Suidicani et al. observed that men with O phenotype had higher risk of IHD (OR=2.1, $p<0.05$) than men with other ABO phenotypes (64). The changes in HRV are not only acute, as Callavari and colleagues observed that the long-duration HRV decreased after exposure, and the most pronounced declines were at night (56). The HRV during the sleeping period is not affected physical activity, which is a predictor for HRV and a potential confounder. Some studies indicate that sleep may be a condition in which HRV best identifies autonomic derangements because sleep is a condition in which cardiac autonomic activity can be studied in the absence of factors including higher cortical factors and physical activity (65).

Even though the scientific evidence suggests that exposure to welding fumes induces changes in biomarkers of heart function, it is of importance to be aware of the problematic interpretation of these changes in relation to the long term effects. For instance, if arterial stiffness is associated with heart disease in one situation, it does not necessarily reflect that in another. Also in the case of the endo-

thelial function which is associated with severity of atherosclerosis, there are situations where an improving endothelial function is not associated with beneficial effects on the heart.

In our analysis of the specific type of outcome, AMI vs. other IHD, we found a significantly increased risk of AMI. The analysis was although only based on three studies, however by the scientific evidence of changes in biomarkers for IHD and CD after short term exposure, it may be plausible that lifelong cumulative exposure to welding fumes can increase the risk for IHD, but we do not have enough evidence to draw reliable conclusions.

10 Conclusion

There is a strong heterogeneity in estimates of risk for IHD according to occupational metal welding across a limited number of observational studies. Although some large higher quality studies indicate a slightly increased risk, these findings are not corroborated by other studies. Overall available data is too limited to draw reliable conclusions as to possible risk of IHD in relation to metal welding. Studies concerning the biological mechanisms by changes in biomarkers of IHD indicate that exposure to welding fumes can induce systemic inflammation and reduce HRV, although the mechanisms are not fully understood.

11 Evaluation

The epidemiological evidence is based upon the systematic review and meta-analysis presented in this report and rated according to the criteria defined by The Danish Society of Occupational and Environmental Health (Appendix 1).

Hypothesis	Issue	Rating according to DASAM criteria
1	The exposure to welding fumes is causally linked to development of ischemic heart disease.	+ (limited evidence)
2	The risk for ischemic heart disease among welders is dependent on the characteristics of the exposure, e.g. material welded, welding method and the length of exposure.	0 (insufficient evidence)
3	Exposure to welding fumes induces changes in biomarkers of heart disease.	+ (limited evidence)

Comments:

Hypothesis 1: Few epidemiological studies indicate a modest elevated risk of IHD among welders but bias and confounding cannot be ruled out with reasonable confidence and results are not corroborated by other studies.

Hypothesis 2: Available data are insufficient to determine if specific welding process are imposing a higher risk than others.

Hypothesis 3: Few experimental studies have reported higher levels of some biomarkers of inflammation in blood and increased HRV. The evidence indicates that exposure to welding fumes has effects on biomarkers for IHD, although it is unknown whether the effects have a negative impact on the health of the welders and in addition, the mechanisms are not clearly understood.

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