Cumulative physical exposure in the work environment as a risk factor for primary osteoarthritis leading to total hip replacement

Exposure assessment and risk estimation

PhD thesis

Tine Steen Rubak

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Preface

The work presented in this PhD thesis was carried out between April 2007 and February 2010 at the Danish Ramizzini Center, Department of Occupational Medicine, Aarhus University Hospital.

I wish to thank my supervisors for their always positive thinking and eagerness to make this a work worth continuing, even after finishing this thesis.
Poul Frost for always having the extra time to listen to me, when I wandered into his office, and thus giving me the opportunity to see things in another perspective. Susanne Wulff Svendsen for her always positive and constructive ideas, and huge linguistic help. Kjeld Søballe for being there, when called upon, and showing me the orthopaedic way.

My gratitude to Michael Væth and Morten Frydenberg for their invaluable statistical help and patience with my countless e-mails and visits.

I also wish to thank my co-authors for their participation in this work with comments, ideas and hard work: Johan Hviid Andersen, Jens Peter Haarh, Ann Kryger, and Lone Donbæk Jensen.

Finally I wish to thank my fiancé and the two girls for keeping up with me, while I was living in Aarhus and our life was somewhere else. My parents for letting me move in (again). Without the help and support from these persons, this would have been a "long days journey into night" instead of a long journey into enlightenment.

Farum/Aarhus February 2010
Tine Steen Rubak

This thesis is based on the following papers:

I. A job exposure matrix based on expert ratings for use in general population studies of primary hip and knee osteoarthritis in relation to physical work loads

II. Risk of total hip replacement due to primary osteoarthritis in relation to cumulative physical work loads: a nationwide cohort study

III. Risk of total hip replacement due to primary osteoarthritis in relationship to cumulative physical work loads: a nested case control study

Contents

Abbreviations

In alphabetic order
AK – Ann Kryger
BMI – body mass index
CRS – Civil Registration System
D-ISCO 88 – Danish version of the International Standard Classification of Occupations
DST – Statistics Denmark
HEG – homogeneous exposure group
HR – hazard ratio
IEM – industry exposure matrix
ISCO – International Standard Classification of Occupations
JEM – job exposure matrix
JHA – Johan Hviid Andersen
JPH – Jens Peder Haarh
kg - kilogram
LDJ – Lone Donbæk Jensen
NPR – National Patient Registry
OA – osteoarthritis
OR – odds ratio
PF – Poul Frost
SES – socio economic status
SHR - standardised hospitalisation ratio
SWS – Susanne Wulff Svendsen
THR – total hip replacement
TR – Tine Steen Rubak

1. English summary

Primary osteoarthritis (OA) is the most common joint disorder in the world. It is also the primary reason why patients undergo joint replacement surgery. In Denmark alone, 7790 hip replacements were performed in 2007, and the number has been increasing during the last decade.

It is a longstanding theory that primary OA the hip is cause by "wear and tear" in the work environment. Outside the work environment several other risk factors have been studied. The strongest of these is age; others include body mass index (BMI), hip injury, childhood hip disorders, and a constitutional predisposition. Several reviews have concluded that there is moderate to strong evidence of a causal relationship between primary OA of the hip and occupational work loads, but they also concluded that there is sparse knowledge of the amount of physical or ergonomical exposure needed to cause primary OA. So far, a dose response relationship has not been well established and the specific risk factors are still being scrutinized. Most studies have had to rely on self-reported exposures, and so far, no study has used independent assessments of cumulative exposure.

This thesis is based on the two epidemiologic studies and the development of two exposure matrices, for the use of studying primary OA of the hip in general populations.

The first study was a cohort study comprising a little more than a generation of Danish men and women with at least ten years of full-time employment, from all parts of the labour market. Cumulative exposure was calculated for all participants, when linking their industry of employment to an industry exposure matrix. For men there was an exposure-response relationship between cumulative exposure and the risk of THR. This was not seen for women.

The second study was a nested case-control study comprising approximately 5500 individuals. Occupational titles was collected and linked to a job exposure matrix, making it possible to calculate cumulative exposure two to 22 years before receiving a total hip replacement. Lifting more than five tons per day, in five years gave an increased risk of 15% of THR for men, but not for women.

We have showed an exposure-response relationship between cumulative physical exposures in the work environment and total hip replacement for men, when using independent exposure assessment.

2. Danish summary

Primær artrose er den mest udbredte led-sygdom i den vestlige verden. Samtidigt er det hovedårsagen til indoperation af kunstige led. Alene I 2007 fik 7790 danskere en ny hofte, og antallet af operationer er steget gennem de seneste 10 år.
I Danmark betegnes primær artrose oftest "slidgigt", hvilket beskriver den generelle forventning om, at sygdommen opstår på grund af fysiske belastninger, hovedsageligt i arbejdet. Der er undersøgt flere risikofaktorer for udviklingen af hofte artrose udenfor arbejdet. Den største risikofaktor er alder. Derudover er body mass index (BMI), tidligere traumer mod hofterne, familiær disposition og medfødte misdannelser risikofaktorer for udvikling af hofte artrose.
Flere nylige reviews har konkluderet, at der er en sammenhæng mellem fysiske belastninger i arbejdet og risikoen for udvikling af hofte artrose. Samtidigt har de påpeget, at det stadig mangler viden om dosis-respons sammenhænge for specifikke belastninger. Derudover bygger de fleste studier på selv-rapporterede oplysninger om eksponeringer, og er dermed præget af informations bias i form a recall-bias.
Denne afhandling bygger på to epidemiologiske studier og udviklingen af to eksponeringsmatricer til objektiv vurdering af kumulerede eksponeringer i arbejdet.
Det første studie var et registerbaseret kohorte studie, som inkluderede lidt mere end en hel generation af den danske arbejdende befolkning, med minimum 10 års fuldtidsansættelser. Kumuleret eksponering blev beregnet ved at koble den branche, hvori ansættelse var sket, til en branchematrice. For mænd var der en tydelig sammenhæng mellem stigende fysisk eksponering og risikoen for at få udskiftet hoften. Dette sås ikke for kvinder.
Det andet studie var et case-kontrol studie, med ca. 5500 personer, ligeligt fordelt på mænd og kvinder. Her blev specifikke job titler koblet med en job eksponeringsmatrice, udviklet til studier i hele befolkninger, og kumulerede eksponeringer blev beregnet for de seneste to til 22 år før en eventuel operation. Ved løft af mere 5 tons per dag gennem 5 år, havde mænd 15 % større risiko for at modtage en kunstig hofte i forhold til dem, der ikke løftede. For kvinder fandtes der ikke en sammenhæng.

Studiet viser en sammenhæng mellem fysiske belastninger i arbejdet og risikoen for total hofte alloplastik, for mænd, ved brug af uafhængige eksponeringsmål.

3. Introduction and background

Primary osteoarthritis (OA) is the most common joint disorder in the world (1). All joints are susceptible, and risk factors differ between the joints (2). It has been estimated that work related OA contributes to about 9% of the total costs for all OA (3), showing that work related OA has a high impact, not just for the individual, but also in an economical perspective. In the US alone, the combined number of knee and hip joint replacements performed is in excess of 350 000 annually (1).
Pain and disability are the most important indicators for surgical intervention (4), and the relevance of radiographically defined OA in terms of symptomatic disease burden or health economics is uncertain (5).
Primary OA of the hip is a major cause of morbidity and disability in the elderly, and the problem will increase with the aging population in the Western societies (6). The working age population is also affected (7). According to the Danish Hip Arthroplasty Register, 50.8% of all hip arthroplasty operations in 2007 were performed on persons under the age of 70, and 77.6% were due to primary OA (approximately 3030 operations) (8).
Total hip replacements (THR) represents the end stage disease of primary OA of the hip (9). End stage OA is of public health concern in Western societies with influence on physical capacity among working aged people as well among the elderly. Although THR is considered an effective and safe treatment, complications occur in relation to operations and anaesthesia. In Denmark 27% of patients were registered to have blood transfusions within the first 7 days after THR in 2006 and within ten years 15% of operated patients underwent revision (8). Perioperative mortality has been reported to be around 0.5% within three months in patient groups with a mean age of 64 years (10). Therefore, from public health perspectives as well as due to risk of complications in relation to THR, and the need of revisions, it is important to identify modifiable risk factors of THR. Other risk factors include age body mass index (BMI) (11-13), hip injury, and a constitutional predisposition (14). Another reason for choosing THR as outcome is the fact that most patients with primary OA are not found in registers of hospitalisation, since they are mainly treated at their general practitioner. The diagnosis of primary OA given at a practitioner is

sometimes based on clinical findings, and not further examined in a hospital setting. This makes it hard to study the whole population, and thus THR is the choice for register-based studies. Other outcome criteria have been used, namely radiographic OA (15-22), clinical OA (23-26), or being on a waiting list for THR (12;27;28). Patients on a waiting list might differ from those actually receiving surgery, if those in employment are moved forward on the list compared to retired persons. Then the waiting list patients would tend to be older, or have a more loose connection with the labour market, making it difficult to study occupational exposures.

It is a longstanding theory that mechanical wear and tear through life is a contributing cause of primary OA (29). If this were indeed the case, then cumulative exposures in the work environment would be more reasonable to study than exposures immediately leading up to diagnosis or surgery. Several reviews have concluded that there is moderate to strong evidence of a causal relationship between primary OA of the hip and occupational work loads (6;30-32). These reviews agree that there is sparse knowledge of the amount of physical exposure needed to cause hip OA due to few longitudinal studies (11;15;25;33-36), and less adequate exposure assessment. Longitudinal studies have used job titles as such (15;34-36), or crudely classified by the researchers into a few broad exposure groups without assessing cumulative specific exposures (25;33), or they have relied on self-reported biomechanical exposures (11). From these studies, it is not possible to determine exposure-response relationships regarding cumulative exposures. Case-control studies have been of rather small sample sizes with less than 1000 subjects included. Some also used job titles alone (37;37), or broad exposure groups based on job titles with assessment of cumulative exposures (20). Others relied on self-reported exposures (12;21;22;27;28;36).

Evidence of association between hip OA and physical occupational exposures, literature review 1985 – 2009

The latest thorough review of occupational exposures and the risk of hip OA was published in 2008 by Jensen (30). The references in the review was used, and a literature search was performed in Medline with the following search terms osteoarthritis, osteoarthritis, hip, occupation, work, occupational exposure, work load, and physical exposure to find new articles not included in the review. This yielded three new studies, published 2008-2010.

In **Appendix A table 1A** an overview of the different studies is given with emphasis on exposure assessment versus outcome assessment, as well as study design. It can be seen that the majority of all studies have relied on self-reported exposures, no matter what outcome has been the point of interest and no matter the study design.

A summary table of the studies is presented in **Appendix A table 2A**. The summary is broken down by outcome, where THR is the main point of interest.

"Hospitalisation due to primary OA" is described together with THR, because most primary OA patients are seen in outpatient clinics, and the main reason for hospitalisation is joint replacement surgery. Hence, hospitalisation is here seen as a synonym for replacement surgery. For each study, a short note on strength or weakness is reported.

In the next paragraph, emphasis will be given on those who have looked into exposure-response relationships, while studies without only will be listed.

Only two studies have investigated aggregated (cumulative) loads in relation to the risk of THR (38;39). The two case-control studies are very similar in their design, and use of self-reported exposures, but differ by studying men (38) and women (39) separately.

For men exposures are reported as hours per week of e.g. sitting or standing, kg lifted per week, and times lifting 40 kg per week. For women exposures were assessed per day (sitting, standing) and number of heavy lifts per day (no reports of the weight of items lifted). Exposures were aggregated, and three levels (low, medium and high) were created. The actual cut-off points are listed in the papers, but have not been used for establishing safe exposure levels. This might be because the ranges within the three levels are fairly wide, and thus a specific level is difficult to calculate. For men (38) an increased risk with both amount of tons lifted (1.58 medium level, and 1.84 high level) and times lifting more than 40 kg was seen. (1.38 medium level and 2.40 high level) For women (39) heavy lifting yielded an increased risk ranging from 1.1(medium) to 1.5 (high), yet not statistically significant. Both studies had fairly few participants (approximately 240 cases and 300 controls), and were restricted to cases referred to hospitals in urbanised settings, and controls from either same referral areas or whole counties surrounding the hospital referral areas. So far only one other study have shown an exposure-response relationship between physical loads and THR (11). Self-reported physical exposures the year before screening for cardiovascular diseases were grouped into four levels (sedentary, moderate, intermediate, intensive). This showed an increasing risk of THR with increasing exposure for both men (1.5, 1.7, and 2.0) and women (1.1, 1.4, and 2.1). For women only the intensive group yielded a statistically significant OR. This was a cohort study of approximately 50.000 persons, with nine years of follow-up in Swedish national registers. However, the number of cases was fairly small (382 women, 268 men). Again, no safe exposure levels could be established due to qualitative exposure assessment.

Studies of farmers (16;21;37) have showed an increased risk with increasing time employed in farming. After 10 years of farming the OR ranges from 1.67 (21) to 9.3 (16). These two studies have used radiographic OA as outcome and self-reported job title as exposure assessment. When using THR as outcome the OR after 10 years of farming is reported to 3.2 (37), but looking at a more detailed grouping of time spent in farming an exposure-response relationship was not seen.
The tendency is a higher risk for farmers with increasing years spent in farming, no matter the outcome studied.
Heavy lifting have been investigated both for men and women (12;17;18;27;28;38-40). Two studies have looked at approximately the same weights being lifted (17;27), and they reported an exposure-response relationship with OR ranging from 0.8 (0.1 – 9.9 years of exposure, outcome waiting list for THR) (27) to 2.5 (20 years or more of exposure, radiographic OA) (17) for men. For women, Coggon (27) could not present the same exposure-response relationship (OR: 1.1, 1.4 and 0.8 with increasing years of exposure). Lau (12) reported increasing risk of radiographic OA, more pronounced for men (1.9 for 10 kg 1-10 timer per week to 9.6 for 50 kg more than 10 times per week), than for women (0.7 for 10 kg 1-10 timer per week to 2.9 for 50 kg more than 10 times per week). For women the risk was even higher (3.0) when lifting 10 kg more than 10 times per week. The study was performed in a Chinese population,

which could be expected to differ from a Caucasian population, as seen in most other studies. Yoshimura (28) reported risk of being listed for THR for women when main job entailed lifting either 10 kg, 25 kg or 50 kg regularly in main job (1.2, 1.5 and 4.1). Only results on 50 kg were statistically significant. This was the second study performed in an Asian population.

From these studies it have not been possible to establish a threshold, and for women there seems to be little evidence of heavy lifting being a strong risk factor, not even when using aggregated exposures.

Several studies have studied heavy work (in various definitions) (11;20;23-25;36;40;41). For two of the studies (24;25) it is difficult to distinguish between men and women. Both show an increasing risk of clinical OA with increasing exposure (2.7 (24) and 6.7 (25) for the highest exposure groups).

When grouping self-reported occupational histories into 3 levels, Roach (20) reported an exposure-response relationship between exposure and the risk of radiographic OA (1.9 – 2.4). Another 3 level grouping was studied by Vingård (41). Here an exposure-response relationship for receiving disability pension (4.1 – 12.4) was seen. Both studies only comprised men.

For men there is an increasing risk with increasing exposure of heavy work. Nevertheless, none of the studies can point to specific exposures in the heavy work to be responsible for the increased risk. For women the evidence is sparser.

The majority of studies have relied on self-reported exposures, especially problematic in case-control studies, where re-call bias tends to overestimate risk estimates. With quantitative self-reported exposures of amount lifted, it seems that using radiographic OA as outcome yields higher risk estimates than when using being put on a waiting list for THR. The same pattern is seen, when using amount of time spent in farming. The picture is more uneven, when studying heavy jobs, here clinically assessed OA yields the overall highest risk estimates for the highest exposure. Thus, no common pattern is seen in the studies with regard to exposure-response estimation. Hence, there is limited evidence to establish preventive guidelines, if indeed needed. Independent exposure assessment is needed, to establish safe exposure levels.

4. Aim of the thesis

1. Development of a job exposure matrix covering the entire Danish labour market, independently assessing six generic exposures to the lower extremities.

2. Testing the hypothesis that increased cumulative physical work loads are a risk factor for primary OA leading to THR. The hypothesis was tested in two studies:

A) A register-based cohort study, investigating cumulative combined physical load as risk factor for developing primary OA leading to THR.

B) A nested case-control study, exploring specific exposures (standing, and heavy lifting) in the work environment in relationship to the risk of receiving a THR due to primary OA.

5 . Exposure matrices

In order to establish independent exposure assessments, we developed two exposure matrices concerning exposures to the lower extremities. Other available methods for quantitative assessment of physical exposures include expert ratings, self-reports, systematic observations, and direct technical measurements (42). Self-reported physical exposures have unique advantages for a number of applications (43), and have been widely used even in recent studies (44). However, self-reported exposures entail validity problems to the extent that individuals with pain overestimate their exposures leading to inflated estimates of exposure-response relations (45). The evidence-base for a causal relationship between symptomatic primary hip OA and occupational physical exposures would be enhanced by studies using quantitative measures of generic exposures that are assessed independently of the musculoskeletal symptom status of the individual.

In general population studies, systematic observations and direct technical measurements are resource demanding, even if the methods are only applied to small subsets of the study population. Hence, a JEM is a feasible way to obtain independent individual exposure measures based on information on job titles (46;47), since this information is considered of high validity (48;49). The concept of JEMs was described as early as 1980, and JEMs have proved valuable in occupational epidemiology (50-54). Retrospective exposure assessment is a special challenge(55) and for this purpose expert rating may often be the best method available (48). Expert rating may be used either on a case-by-case basis (56) or as a means of constructing a job exposure matrix (JEM) (57). On the other hand it has been suggested that expert ratings are overall less useful than direct measurements (58). However, physical exposures have rarely been included in sector specific JEMs (59;60) or in general population JEMs (46;61). An ambitious Finnish general population JEM, FINJEM, covers biomechanical exposures in addition to other physical (noise, light, etc), chemical, microbiological, and psychosocial exposures, but quantitative biomechanical exposure levels cannot be extracted (46). For distal upper limb exposures, the first steps have been taken to construct a general population JEM based on direct technical measurements (62;63).

One general population JEM focuses on physical exposures to the lower limbs. This JEM was developed by D'Souza and colleagues to take advantage of pre-existing data in the NHANES III study (61). They were restricted by the fact that the 40 job groups were fixed entities developed for other purposes (64). Hence, the job groups were often inhomogeneous as regards exposures to the lower limbs, e.g. one of the groups contained both writers and athletes. Thus some of the jobs were in effect grouped in such a way as to obscure their impact (48;65). The JEM was based on expert ratings of the occurrence of six physical exposures with respect to proportions of the work day (61).

In general, JEMs have the drawback that they do not usually take into account the variability of exposure within occupational classes or job categories (66), and this misclassification of exposures tends to mute the observed risk estimates towards unity (67). On the other hand, if associations between exposures to the lower limbs and risk of replacement surgery can be documented in studies using a JEM approach, this will profoundly corroborate the evidence from previous studies relying on self-reported exposures.

Industry exposure matrix

An industry exposure matrix was developed for the purpose of the cohort study. This is a simple approach to exposure assessment, but useful when only industries of employment and not occupational titles are known.

On the basis of the 112-grouping of industries used by Statistics Denmark (68), three experts, independently, rated the combined intensity of physical hip exposure in each industrial group on a three point scale, 0 (not likely to be exposed), 1 (likely to be exposed at moderate level) and 2 (likely to be exposed at a higher level). The combined exposures that were taken into consideration were standing/walking, whole-body vibration and lifting (primarily total daily loads). The final rating was reached by consensus. An extra group (industry not stated) had to be created, since some companies had no industry code, only name of company, registered.

Job exposure matrix

For the nested case-control study a job exposure matrix (JEM) was developed. In order to establish a JEM covering the general population, the starting point was the list of the 2227 occupational titles (353 classification numbers) in the Danish version of the International Standard Classification of Occupations (D-ISCO 88) (69). The D-ISCO 88 is slightly different from the international version (ISCO) (70) - some English titles do not occur in the Danish version and some Danish titles have no counterpart in the international version. It is worth noting that some titles have differing ISCO classification codes in the two versions, for instance, "furniture mover" has code number 9330 in D-ISCO 88 and 9333 in ISCO, and "cutter, fish" has code number 8271 in D-ISCO 88 and 7411 in ISCO. We report our JEM with international occupational titles and classification codes, where possible.

The complete list of occupational titles was screened to exclude obsolete or very rare titles, and to identify occupations with minimal exposures to the lower limbs. To be considered more than minimally exposed, at least one of the following exposures had to be present in the job: standing/walking at least six hours a day, sitting more than six hours a day, kneeling/squatting more than half an hour a day, exposure to whole body vibration more than two hours a day, lifting more than two tons a day or lifting burdens weighing 20 kg, or more, at least 10 times a day. Cut-off levels were chosen according to earlier studies (12;17;18;39;71-73). For sitting, we defined the cut-off level higher than earlier studies (71;74). Thus, prioritizing specificity rather than sensitivity (52;75). Driving tractors and heavy machinery (i.e. road rollers and excavators) was considered to entail whole body vibration, whereas riding cars, lorries, trucks, and trains was not. These decisions in accordance with the findings by Palmer et al. (76), since we expect the English and Danish labour market to be of similar appearance concerning whole-body vibration. Two occupational physicians checked the initial decisions and the few disagreements were settled by consensus.

Establishing homogeneous exposure groups

Exposed job titles were collapsed into homogeneous exposure groups (HEGs) with respect to all exposures that we intended to assess (77;78). Job titles with the same D-ISCO 88 classification number were not grouped together if their exposures were judged to differ, e.g. paviours and stonemasons were classified in different groups. On the other hand, several different D-ISCO 88 classification numbers could be categorised in the same group. The grouping of job titles was discussed in the exposure assessment team. Any disagreements were settled in consensus.

Expert rating of HEG exposures

The exposure assessment team comprised five persons (PF, SWS, JHA, JPH, and TR). The number of experts in the panel was chosen in accordance with recent recommendations (79;80). For each HEG, ratings on sitting, standing/walking, kneeling/squatting, and whole-body vibration were done in half-hour intervals. Experts rated the mean number of hours per day, and what they expected to be the minimum and maximum number of hours per day. Standing/walking, sitting, and kneeling/squatting should add up to a full workday, defined as an eight-hour shift. For lifting, they stated the mean, minimum and maximum number of kg lifted per day, and the mean, minimum and maximum frequency of lifting burdens weighing 20 kg or more. We were interested in exposure levels, frequencies, and durations (42;81). We also wanted some indication of variation within groups. Ratings were compared and gross outliers were discussed at a meeting between all five experts. Most disagreements arose due to misinterpretation of job titles and components of the jobs. After reaching a consensus on job components, two HEGs were re-evaluated. For each HEG, the final level of exposure was defined as the mean of the five independent ratings. In this way we aimed to synthesize the best features of panel team work/consensus ratings and independent assessments (61;80;82).

Inter-rater agreement

Graphic evaluation was used when examining inter-rater agreement. This allowed assessment of systematic disagreements with the same experts tending to rate above or below the mean. A kappa statistic cannot be used for simultaneous comparison of more than two raters or groups of raters. We chose to look at the individual ratings in comparison with the mean for the occupational job title group. Correlations between different assessment methods are affected by the amount of variability present in the variables being compared (43), and looks at the degree of association, not agreement, and is thus inappropriate for the study of inter-rater agreement (83).

Validity

To validate the JEM, in the absence of a gold standard, we ranked the job groups according to their mean exposure levels for each exposure variable. The rankings were divided into 4 or 5 levels (paper I). Two other experts (AK, LDJ), who were not involved in the expert rating of HEG exposures, stated their agreement of the rating, and suggested adjustments, if any.

6. Design and methods in the two studies

National Registers

All individuals born in Denmark or with permanent residency in Denmark has a unique number in the Civil Registration System (CRS) (84). This number is used for all encounters with the Danish healthcare system and other official registers. It is thus possible to link different registers at the individual level.

The CRS register includes information on date of birth, current residence, date of emigration, date of death, "protection against inquiries in connection with scientific studies", and "protection of address".

From the Danish Labour Market Supplementary Pension Scheme (85) information on amount of employment and industry of employment for each year since 1964 was collected. All companies in Denmark are obliged to report to this register. Self-employed are not included in this register, unless they have been employed at another company before starting their own business. Individual employment industry, company, and degree of employment (a degree of 100 equals full-time employment) are registered on yearly basis.

The National Patient Registry (NPR) contains information on all somatic inpatient admissions to Danish hospitals since 1977. It is possible to get information on diagnosis, surgery performed, and date of discharge, among other things. The register has a high degree of completeness and agreement with medical records.(86)

We used ICD-8 diagnoses (osteoarthrosis coxae - 713.00) to identify diagnoses before January 1, 1996, and ICD-10 after January 1, 1996 (arthrosis coxae primaria - M16.0, M16.1, M16.9). Surgical procedures were coded in accordance with the NOMESCO Classification of Surgical Procedures (hip replacement surgeries - KNFB20, KNFB30, KNFB40, KNFB99) (87).

Study-base

The cohort and the case-control study used the same underlying study-base. It consisted of all persons born in Denmark between January 1, 1925 and December 31, 1964. When coupling several national Danish registers, the final population consisted of all with at least ten years of full-time employment between 1964 and 2006, both included, who had not received a THR before January 1, 1996.

Register-based cohort study

Study-population

From the study-base we excluded all who had registered as claimers of "protection against inquiries in connection with scientific studies", all who did not reach 10 years of full time employment between 1964 and 2006, all living in Greenland, all who had received a THR, emigrated or died before reaching 10 years of full time employment or before January 1, 1996, or with missing information of socioeconomic status. A few persons turned out to be registered with more than two full time jobs per year. These were excluded, since we could not confirm their employment status elsewhere.

Sample size

Sample size was determined by register information, to contain as large a part of the Danish working population as possible, within the age group, where THR is performed on a regular basis.

Outcome

Cases were defined by the first registration of THR due to primary OA in the NPR between January 1, 1996 and December 31, 2006.

Exposure

Cumulative exposure was calculated for the entire work-life when by linking industry and degree of employment to the IEM on an individual level (see chapter 7, "use of the IEM" for example). For all persons in the cohort it was possible to accumulate exposure during follow-up.

Follow-up

The cohort was followed-up in the NPR from January 1, 1996, until receiving a THR due to primary OA (becoming a case), receiving a THR due to other circumstances, emigration, or death (censoring), or December 31, 2006 (end of follow-up), whichever came first.

Other variables

Information on socioeconomic status (SES) was gathered from Statistics Denmark (DST). For each person SES was collected for 1980, 1986, 1996 and 2006 to obtain SES in the age span from 40-55. SES from 1980 was used for those born 1925 – 1935, 1986 for those born 1936-1945, 1996 for those born 1946 – 1955, and 2006 for those born 1956-1964. If SES for the relevant year was missing, the nearest informative SES was used (paper II).

We grouped the SES from DST into 5 levels in the following way: group 1 included self-employed and their spouses; group 2 included top leaders in business and organisations and highly skilled white collar workers; group 3 included white collar workers and skilled blue collar workers; group 4 included unskilled blue collar workers and workers without mention of skill level; group 5 included persons outside the labour market.

Nested case-control study

Candidate population.

The case-control study was nested within the cohort from paper II. A few modifications were done. To be eligible for the case-control study, participants could not have received a THR before January 1, 2005. Death, emigration, "protection against inquiries in connection with scientific studies", or "address protection" before December 1, 2008 also lead to exclusion.

Case definition

Eligible cases were all new cases of first registered THR due to primary OA in 2005 and 2006 according to the NPR in the candidate population.

Controls

Eligible controls were all in the candidate population who had not received a THR at the date of surgery for the case, for which it was sampled.

Sampling

Cases and controls were sampled in a density sampling (88) from the underlying candidate population, and matched on gender and date of birth at the day of surgery. Thus, a control can be used as control more than once, and even become a case later on. Cases were sampled at randomly, not chronologically by date of surgery or by age. STATA program code for sampling can be found in **Appendix F**.

Sample size

The population size was chosen to allow exposure-response analyses.

Questionnaire

A questionnaire was constructed for the purpose of this study. Among other things, the questionnaire asked for the Danish occupational title of their main occupation in specific time periods (2000-2007, 1990-1999, 1980-1989, and overall before and after 1980). Main occupation was defined as the job, held for the longest time in the specified time period. Highest level of education and first year in the labour market were also collected.

Questions of earlier traumas towards the lower extremities, and the year of such trauma were included. Background information on height, weight (present and at 25 years of age), smoking habits, co-morbidity (diabetes, thyroid disease, rheumatic arthritis, osteoporosis), and familiar predisposition were asked for as well. Sporting activities at the age of 25 was scrutinized both in amount of time, and type of sports. Even though we aimed at using independent exposure assessments, we asked for self-reported exposures as well. For the overall main occupation stated, we asked for time spent standing/walking, driving heavy machinery, and sitting. Answers were given in five distinct levels. For lifting, we asked if there had been lifting of objects weighing less than 10 kg, between 10 and 20 kg, and 20 kg or above. Answers were given in four distinct levels.

We made an effort to construct the questionnaire in a way not to reject controls from answering, e.g. by appearing to study overall health and not primary OA or THR. The questionnaire was mailed in January 2009, and up to two reminders were sent to non-responders.
The full questionnaire, in Danish, is shown in **Appendix B**.

Occupation

Self-reported occupational titles were coded into D-ISCO 88 (69). This was done by research assistant with experience from several industries within the Danish labour market. In this way we complied with the advice by Kromhout (49) that recoding should be done by trained coder a with a basic knowledge of jobs performed in agriculture, construction, industry and services.

Exposure

The total amount of years of employment within was extracted from employment information in the Danish Labour Market Supplementary Pension Scheme, and applied to all participants in the study, for the time period from 1980 to 2005 (both included).
Cumulative physical exposure was assessed for up to 20 years, disregarding the last two years before THR for cases and to the same year for matched controls by combining information of time in specified occupational titles to the JEM. In this way those THR cases appearing in 2005 and their matched controls, cumulated exposure from 1983 to 2002 (both included).
We constructed exposure variables for standing/walking, amount of manual lifting, frequency of manual lifting of objects weighing 20 kg or more, and for whole body vibration in the same manner as pack-years are calculated from information of mean daily tobacco consumption and years of smoking to express a cumulated dose. In this way standing/walking 6 hours per day for one year, defined one standing-year. Exposure to whole-body vibration for one hour per day during one year, defined one vibration-year. Lifting 1000 kg per day for one year defined one ton-year, and lifting objects of 20 kg or more 10 times a day defined one lifting-year.
Cumulative exposure was calculated for each of the four exposure variables.

Ethics

In accordance with The Danish National Committee on Biomedical Research Ethics, studies only involving register-based data or questionnaire data are not obliged to be notified to the local committee (89).

The study was approved by the Danish Data Protection Agency.

Analysis

Register-based cohort study

Data was analysed by multiple logistic regression using Stata10 SE (90). The usage of multiple logistic regression in accordance with Richardson (91) equals survival analysis when using Cox-regression and yields a hazard-ratio, interpretable as an incidence rate ratio. For each THR, cumulative exposure estimates for the risk set (persons who were alive and being observed in the study at THR date of the case) were based on the exposure history up to the date of THR of the case. Cumulative exposure was categorised in groups. Persons with a cumulative exposure of zero was grouped into one group and used as reference group. There were five groups for women and six groups for men. In this way, we utilised the fact that men had higher cumulative exposure. Since no one has used accumulated exposure in the same manner as us, we had to decide on the cut-off levels without regard to any other findings. The final cut-off points were as follows (with highest "point-year" reported) 0, 5, 15, 25, 35, 90. The cut-off levels were decided upon the background of the distribution of "point-years" in the two genders separately, ending with common levels for both genders. The highest exposure group for women had 25 point-years as cut-off level. Levels were chosen in order to establish exposure groups of approximately same size, but at the same time ensuring exposure-contrast. A continuous variable in five "point-years" increments was also constructed.

Odds-ratios and 95% confidence intervals (CI) is reported for the explanatory variables fully adjusted model (paper II). Odds-ratios for age-adjusted analysis are reported as well. Stata programming code for creating dataset for analysis and the actual analysis can be found in **Appendix F**.

In order to investigate if a threshold were present, we divided the population into 10 groups, one group including all subjects with an exposure in point-years equal to zero, and 9 groups of equal size for the rest of the population. A multiple logistic regression was done for point-years, including the same confounders as mentioned above. On the calculated odd-ratios, we did a spline regression in five bands to create graphs for the relationship between cumulative exposure in point-years and risk of THR for both men and women. A rough estimate of etiologic fraction was done based on the spline regression graph.

Nested case-control study

Data was analysed with conditional logistic regression in Stata 11(92) in accordance with Breslow (93) and Langholz (94). Analysis yield an OR interpretable as risk ratio (95).

Explanatory variables was analysed independently, adjusted for an a priori fixed set of confounders (paper III).

The total study population, women and men separately were analysed, in accordance with recommendations by Messing and Silverstein (96).

Odd-ratios and 95% CI for explanatory variables have been adjusted for all confounders. When reporting adjusted OR and 95% CI for confounders, they have been adjusted mutually and for standing-years. When using ton-years or lifting-years OR and 95% CI did not differ from results when using standing-years.

Stata programming code for the actual analysis can be found in **Appendix F**.

In order to investigate if a threshold were present, we divided the population into 10 groups, one group including all subjects with an exposure in ton-years equal to zero, and 9 groups of equal size for the rest of the population. A multiple logistic regression was done for ton-years, including the same confounders as mentioned above. On the calculated odd-ratios, we did a spline regression in 10 bands to create graphs for the relationship between cumulative exposure in ton-years and risk of THR for the total case-control population, men and women.

7. Results

Industry exposure matrix

The final IEM

The industry exposure matrix consists of 113 groups – the 112 groups from Statistics Denmark, and the group with no industry code reported in the Danish Labour Market Supplementary Pension Scheme. In the lowest exposure group, there were 32 industries, 56 in the intermediate, and 25 in the highest exposure group. Industries with no or low exposure were e.g. "manufacturing of medical and optical instruments" and "real estate agents". Intermediate exposure industries were e.g. "restaurants" and "hospital activities". Industries with high exposure were e.g. "refuse of disposal and other activities" and "general contractors".

The final matrix can be seen in **Appendix C**.

Use of the IEM

When using the IEM, only the industry of employment and the degree of employment for each year is needed to calculate the cumulative exposure.

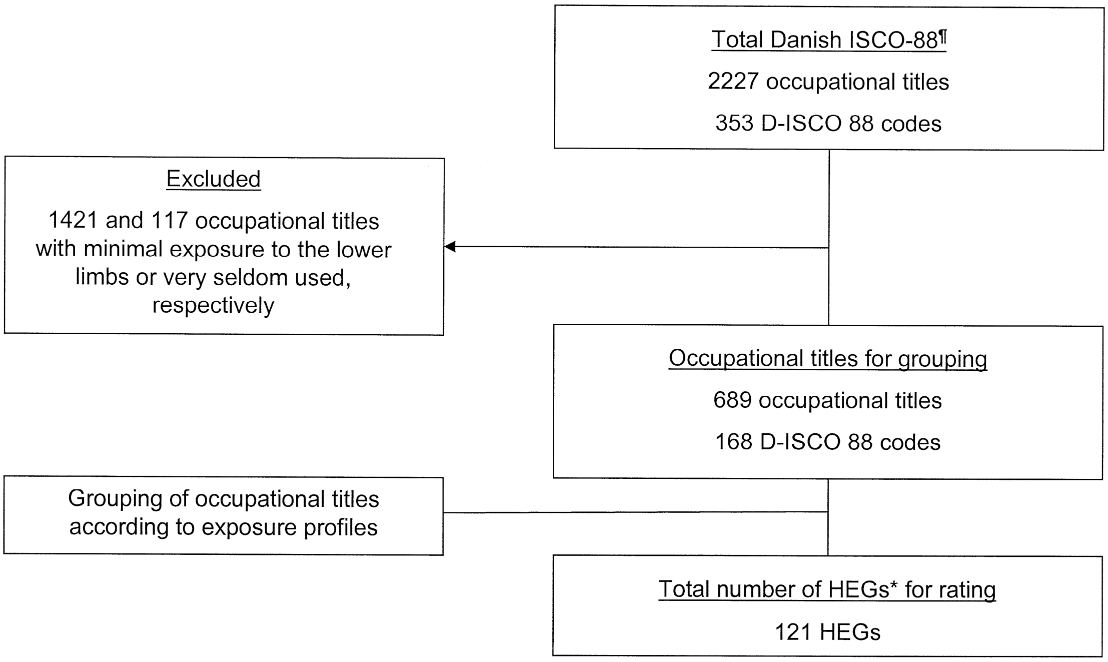
To give an example, a person who had worked full time for four years in an industry where high exposure is likely, worked part time (50%) for six years in an industry where moderate exposure is likely, and finally worked over time (120%) for 10 years in an industry where exposure is unlikely would obtain a cumulative score of exposure of 11 point-years ((4 years * 100% * 2 points) + (6 years * 50% * 1 points) + (10 years * 120% * 0 points) = 11 "point-years")).

Job exposure matrix

The final matrix

A total of 689 Danish ISCO occupational titles were grouped into 121 HEGs. Occupational titles expected to be obsolete or very seldom used amounted to 117 titles, and 1421 occupational titles were screened out as not being exposed above the cut-off levels defined in the six exposure categories.

Figure 1.
The flow of occupational titles and related Danish -ISCO 88 codes to create the final 121 homogeneous exposure groups to be assessed.



¶ISCO-88: Danish version of the International Standard classification of Occupation
*HEG: homogeneous exposure group

Each HEG included from one to 34 different occupational titles. The final matrix cross-classified 121 HEGs with six generic exposures. Some HEGs turned out to be less exposed than the initial cut-off points used to identify job titles with minimal exposures. Exposure estimates of these HEGs were kept in the JEM.

Table 1 depicts the mean, 10^{th}, 50^{th}, and 90^{th} percentile for the six generic exposures

Table 1. Distribution of ratings of six generic exposures in 121 homogenous exposure groups, based on five expert assessments.

Exposure	Mean	10^{th} percentile	50th percentile	90^{th} percentile
Standing/walking, hours/day	5.3	3.0	5.7	6.6
Sitting, hours/day	2.3	0.8	1.9	4.8
Kneeling, hours/day	0.4	0	0.2	1.1
Whole-body vibration, hours/day	0.1	0	0	0.2
Lifting, kg/day	955	193	590	2525
Lifting ≥20 kg, times/day	10.2	1.2	6	21.5

Range of individual assessments among experts is shown in Figure 1H **(Appendix H)** The graphs show the minimum and maximum expert assessments for each HEG in relation to the mean for the HEG, for four of the specific exposures. For "total amount of kg lifted per day" and "times lifting more than 20 kg per day", it is seen that with increasing mean exposure assessment then difference between minimum and maximum also increases. We also did Bland-Altman plots (83) of the difference between expert assessment and mean assessment in relation to the mean assessment and with 95% prediction intervals shown as fitted lines. These plots showed it was not a single expert who constantly was above or below the mean. Plots shown in **Appendix D**.

When translating into English, all 121 HEGs were represented. However, not all 689 Danish occupational titles were translated. Hence, there are only 556 English occupational titles, and 157 ISCO codes. **Appendix E** contains the total JEM.

Face validity

The external experts agreed on the ranking for 707 out of the 726 original ratings (97%). One of the experts had 10 suggestions for change (seven for an increase, three for a decrease of exposure), and the other suggested nine changes (four for an increase, five for a decrease of exposure). None of these suggestions was the same, and we did not change the JEM.

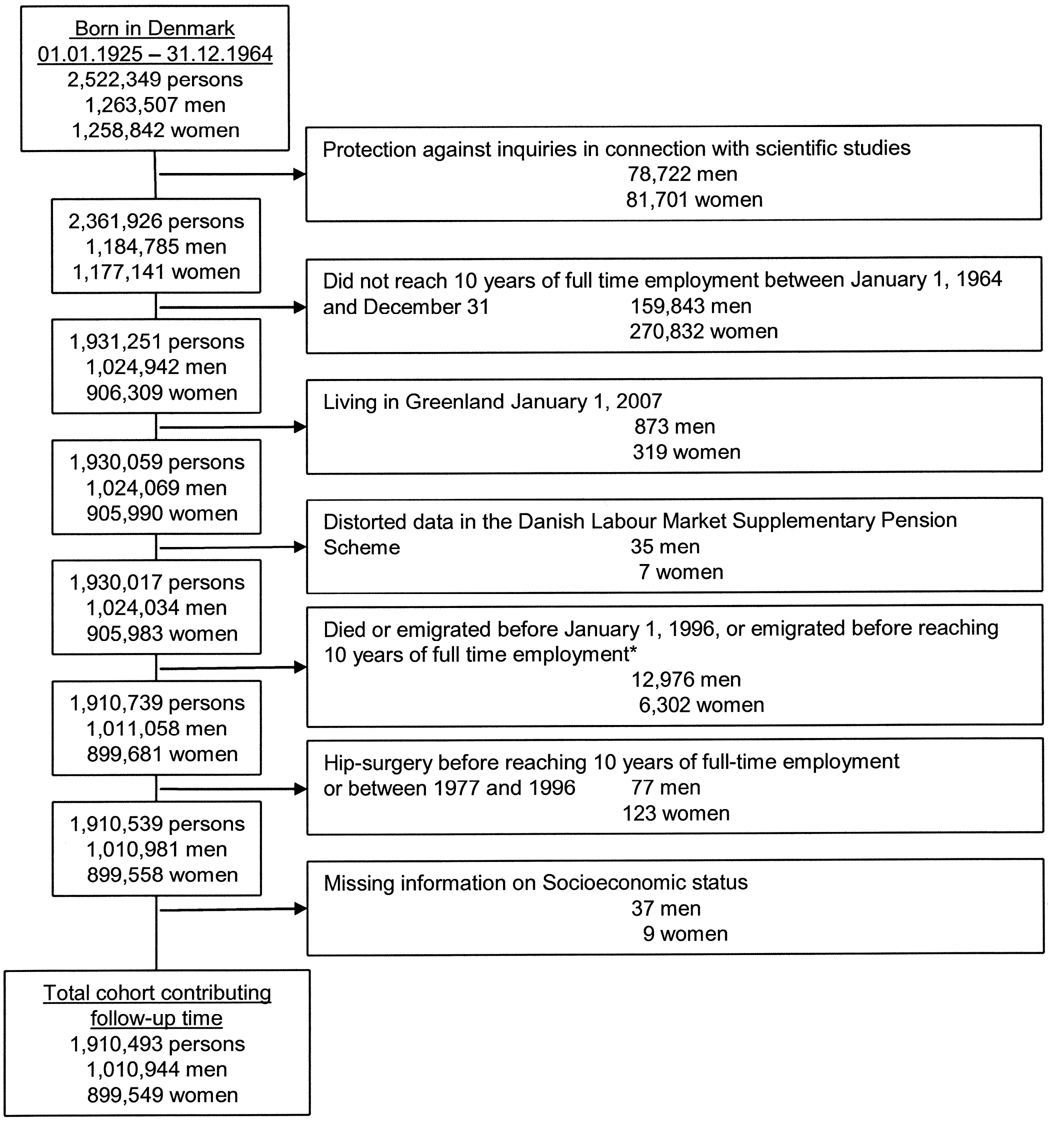
Use of the JEM

When using the JEM, start out with the industry in question. We have used the 9-grouping of Statistics Denmark (68) as starting point. All industries are classified in the following way: "agriculture, fishing, quarrying", "manufacturing", "electricity, gas and water supply", "construction", "wholesale and retail trade, hotels and restaurants", "transport, post and telecommunication", "finance and business activities", "public and personal services", "activity not stated". Having found the industry group of interest, next step is to find the HEG of interest. All 121 HEGs have a heading, describing the job titles included in the HEG. Then it is possible to find the exact job title in question, within the HEG. In this way, we hope to make it easy to use the JEM for other studies.

Register-based cohort study

There were 2,522,349 individuals (1,258,842 women) born in Denmark between January 1, 1925 and December 31, 1964. After exclusion due to the different criteria, 1,910,493 persons (899,549 women) were included in the study. During 9,126,600 person years of follow up 8784 new cases appeared amongst women, and during 10,297,407 person years of follow-up 9900 new cases amongst men.

Figure 4.
Flowchart: from Danish adult population to study population



* It was possible to have emigrated from Denmark, but still work in a Danish company, and thus be registered in the Danish Labour Market Supplementary Pension Scheme.

Women were on average 48.2 years of age at start of follow-up, approximately one year younger than the men were. Men had on average a higher accumulated exposure(17.74 point-years) than women (10.61 point-years), which can be expected in this age group, where at least the women of the older generation were not as active in the work market as the men. Descriptive information of the total population can be seen in tables 1G and 2G in appendix G.

Women

Table 2 shows results of discrete survival analysis for women. No increased risk of THR with increasing cumulative exposures is seen, for neither the grouped variable nor the continuous variable. There was only a very small difference between age-adjusted and fully adjusted analyses. Age was the single most important risk factor for women, yielding an increased risk of 11% per year.

It did not seem that different socioeconomic status (SES) was of importance in relationship to the risk of THR.

Table 2.
Risk estimates of total hip replacement due to primary osteoarthritis for men obtained by discrete survival analysis

Exposure	Hazard ratio		95% CI
	Age Adjusted#	Adjusted*	
Cumulative exposure (point-years)¶			
Reference∫	1.00	1.00	
>0 – 5	1.00	0.96	0.86 – 1.06
>5 – 15	1.00	0.96	0.87 – 1.05
>15 – 25	0.98	0.94	0.85 – 1.04
>25	1.07	0.99	0.90 – 1.10
Continuous in 5 point-year increments	1.00	1.00	0.98 – 1 02
Age (one year continuous increments)	-	1.11	1.11 – 1.11
Socioeconomic status at age 40-55			
Self-employed and their spouses	1.00	1.00	
Top leaders in business and organisations and highly skilled white collar workers	0.81	0.85	0.73 – 1.00
White collar workers and skilled blue collar workers	0.88	0.92	0.82 – 1.02
Unskilled blue collar workers and workers without mention of skill level	0.83	0.86	0.77 – 0.96
Persons outside the labour market	1.09	1.10	0.96 – 1.26

Adjusted for age at start of follow-up
**Mutually adjusted for cumulative exposure, age, calendar year, SES, amount of follow-up and county of residence.*
¶ *Point-years = years of full-time employment weighted by physical exposure in industry of employment*
∫ *Reference: those who have never worked in an intermediate or high exposure industry*

Men

A somewhat other picture was seen for men (table 3). An exposure-response relationship was seen for THR with increasing cumulative exposure. Fully adjusted analyses yielded a lower OR than age-adjusted analyses. Both the grouped variable and the continuous variable showed this relationship.

For men age yielded an increased risk of 9% per year.

SES had a somewhat unexpected outcome. It seemed that with a lower SES there was a lower risk of THR, even when adjusted for cumulative exposure.

Table 3.
Risk estimates of total hip replacement due to primary osteoarthritis for men obtained by discrete survival analysis

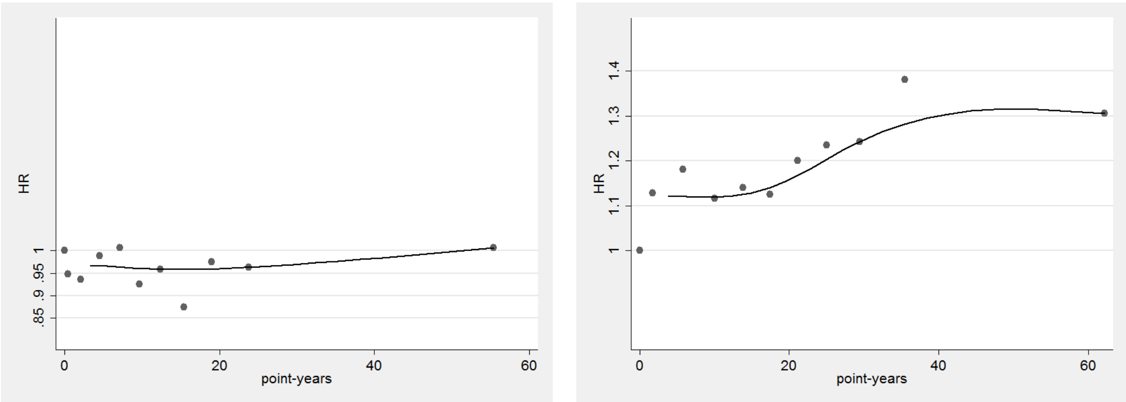
	Hazard Ratio		
Exposure	Age adjusted#	Adjusted*	95% CI
Cumulative exposure (point-years)¶			
Reference∫	1.00	1.00	
>0 – 5	1.25	1.13	0.98 – 1.31
>5 – 15	1.33	1.14	1.00 – 1.31
>15 – 25	1.38	1.19	1.04 – 1.36
>25 – 35	1.44	1.27	1.11 – 1.48
>35	1.60	1.33	1.17 – 1.53
Continuous in 5 point-year increments	1.03	1.02	1.02 – 1.03
Age (one year continuous increments)	-	1.09	1.09 – 1.09
Socioeconomic status at age 40-55			
Self-employed and their spouses	1.00	1.00	
Top leaders in business and organisations and highly skilled white collar workers	0.58	0.63	0.58 – 0.68
White collar workers and skilled blue collar workers	0.72	0.73	0.69 – 0.79
Unskilled blue collar workers and workers without mention of skill level	0.90	0.87	0.81 – 0.93
Persons outside the labour market	0.85	0.87	0.77 – 0.99

 # Adjusted for age at start of follow-up
**Mutually adjusted for cumulative exposure, age, calendar year, SES, amount of follow-up and county of residence.*
¶ Point-years = years of full-time employment weighted by physical exposure in industry of employment
∫ Reference: those who have never worked in an intermediate or high exposure industry

Spline regression showed no threshold for women. Notice that most HRs are below 1.0 and none is statistic significantly different from 1.0. For men, it is seen that a threshold is present approximately at 16-20 point-years. Here after an increase in seen with increasing cumulative exposure until reaching 40 point-years.

Figure 5.
Spline regression for women and men obtained by discrete survival analysis in 10 exposure groups of equal size based on point-years (i.e. years of full-time employment weighted by a point score of physical exposure in employment industries and summarized across all employments since 1964)
● = *Hazard Ratio,* ▬ = *spline regression line*

Women *Men*



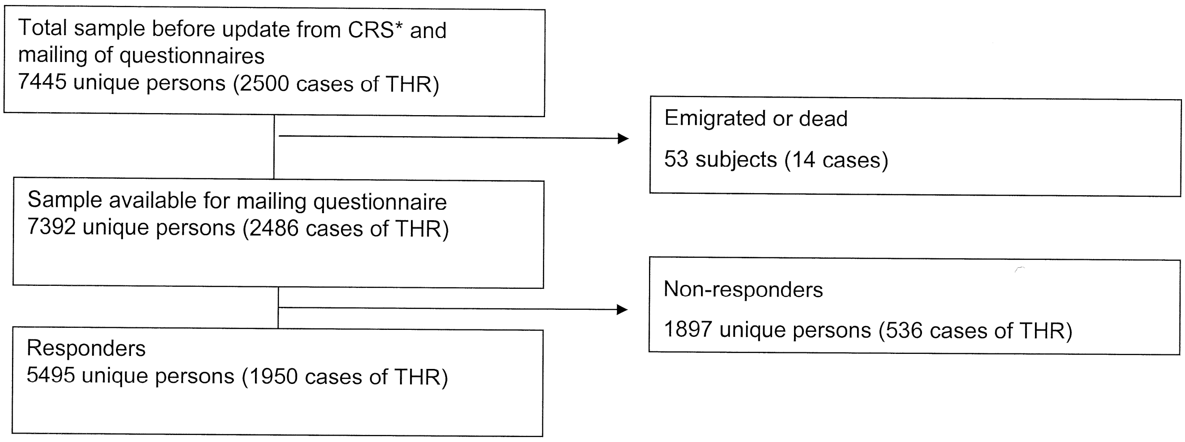
Rough estimates of etiologic fraction (paper II) results in a total of 1138 cases being attributable to cumulative physical loads in the three highest exposure groups, for men.

Nested case-control study

During 2005 and 2006, 4410 new cases occurred, and 2500 matched case-control sets were sampled.

The 2500 matched case-control sets consisted of 7445 unique persons, and of these 55 had been drawn more than once. Before mailing the questionnaires, we did an update in the CRS on vital status, protection of address, etc. We excluded 53 unique persons, due to either death or change of willingness to participate in scientific studies (14 cases and 39 controls). We mailed a total of 7392 questionnaires, and 5495 questionnaires were returned (74.3% returned questionnaires) The final number of matched sets, available for analysis (i.e. including at least one case and one control) was 1746 sets (69.8%).

Figure 7.
Flowchart showing dropout from initial sample to final responders for unique persons in the case-control study



* Civil Registration System

Table 4.
Age distribution and participation rate in the case-control population, divided on gender and case-status

	Men (N=3675)		Women (N=3825)	
	Controls	Cases	Controls	Cases
START	2403	1218	2503	1268
Age 1.1.2005	64.3 (3.7 SD)	64.3 (3.6 SD)	64.8 (3.6 SD)	64.8 (3.6 SD)
NON REACHABLE	20	7	19	7
Age 1.1.2005	64.3 (4.1 SD)	65.3 (2.7 SD)	64.8 (3.4 SD)	65.4 (2.7 SD)
NON RESPONDERS	580	225	704	297
Age 1.1.2005	64.1 (4.3 SD)	64.4 (3.8 SD)	65.2 (3.5 SD)	65.2 (3.8 SD)
RESPONDERS	1803	986	1780	964
Age 1.1 2005	64.4 (3.5 SD)	64.3 (3.7 SD)	64.7 (3.7SD)	64.7 (3.6 SD)
Answers of eligible	75%	81%	71%	76%

A tendency for the youngest women, and the oldest men to participate was seen, for both cases and controls.

A minor part of those not participating, gave a reason for this. For women, two stated multiple sclerosis, three dementia/Alzheimer's disease, 12 stated other illness, and for six women their family reported that they had recently died. For men, one stated dementia, seven stated other illness, and five had recently died. We have no knowledge of the reason for not participating for the rest of the non-respondents.

Descriptive information on the respondents is seen in **table 3G** in **appendix G**. For some variables, we have no missing information. We expected those, who did not answer any questions on smoking, familiar predisposition, and earlier fractures towards the lower extremities, to be non-smokers, to have no familiar predisposition, and not having had an earlier fracture.

Table 4G in **appendix G** contains information on the distribution of participants according to exposure levels for the four exposure variables standing-years, vibration-years, ton-years, and lifting-years.

Total case-control population

For the entire case-control population results of conditional logistic regression is shown in table 6. An increased risk of two percent was seen with an increase of five ton-years or five lifting-years. Self-reported lifting showed an exposure-response relationship. The single most important risk factor was BMI above 30.

Table 6.
Risk estimates, total case-control population, estimated by conditional logistic regression (n= 3584)

Exposure	Univariate OR	Adjusted# OR	95% CI
Standing-years (5 year increase)	1.02	1.00	0.96 – 1.04
Ton-years (5 year increase)	1.03	1.02	1.00 – 1.04
Lifting-years (5 year increase)	1.03	1.02	1.00 – 1.05
Smoking 5 pack-year	1.00	1.00	0.98 – 1.01
Earlier trauma	1.51	1.49	1.23 – 1.80
Familiar predisposition	1.75	1.66	1.24 – 2.22
Type of sport			
Endurance sport	1.17	1.15	0.96 – 1.39
Combination of endurance and risk sport	1.54	1.58	1.30 – 1.92
Contact/risk sport	1.32	1.31	1.06 – 1.61
Co-morbidity	0.78	0.68	0.53 – 0.89
BMI at 25			
<18.5	0.53	0.52	0.35 – 0.77
18.5 - <25	1.00	1.00	
25 - <30	1.29	1.30	1.07 – 1.57
30+	2.32	2.78	1.81 – 4.28
Self-reported lifting			
0 ton years	1.00	1.00	
1- <10 ton years	0.96	0.85	0.60 – 1.21
10- <50 ton years	1.38	1.36	1.09 – 1.68
50+ ton years	1.65	1.37	1.06 – 1.77
Ton-years(5 year increase)	1.01	1.01	1.00 – 1.02

 # Explanatory variables are adjusted for smoking, earlier fractures, familiar predisposition, type of sports, co-morbidity, BMI at 25, whole-body vibration and geographical region.
Confounders are mutually adjusted and adjusted for standing-years.

Women

For women no relationship between increasing cumulative exposure and the risk of THR was seen, for neither univariate or adjusted analyses (table 7). Self-reported exposures showed an un-even pattern, but risk estimates was not statistically different from unity, except for those with a cumulative exposure of 1-9 ton-years, which had an overall lower risk. BMI showed an increasing risk of THR with increasing BMI above normal, and decreasing risk with a BMI below 18.5.

Table 7.
Risk estimates of THR for women, estimated by conditional logistic regression (n= 1629)

Exposure	Univariate OR	Adjusted[#] OR	95% CI
Standing-years (5 year increase)	1.03	1.00	0.94 - 1.06
Ton-years (5 year increase)	1.02	0.99	0.94 - 1.04
Lifting-years (5 year increase)	1.02	0.98	0.93 - 1.04
Smoking 5 pack-year	1.02	1.01	0.97 - 1.04
Earlier trauma	1.55	1.57	1.17 - 2.11
Familiar predisposition	1.72	1.75	1.15 - 2.66
Type of sport			
Endurance sport	1.21	1.20	0.94 - 1.54
Combination of endurance and risk sport	1.41	1.55	1.12 - 2.13
Contact/risk sport	1.26	1.14	0.79 - 1.65
Co-morbidity	0.69	0.54	0.37 - 0.80
BMI at 25			
<18.5	0.58	0.57	0.38 - 0.87
18.5 - <25	1.00	1.00	-
25 - <30	1.22	1.24	0.87 - 1.77
30+	3.49	5.69	2.40 - 13.50
Self-reported lifting			
0 ton years	1.00	1.00	
1 - <10 ton years	0.61	0.50	0.26 – 0.98
10 - <50 ton years	1.30	1.33	0.91 – 1.95
50+ ton years	1.48	0.87	0.50 – 1.51
Ton-years (5 year increase)	1.01	0.99	0.97 – 1.01

[#] *Explanatory variables are adjusted for smoking, earlier fractures, familiar predisposition, type of sports, co-morbidity, BMI at 25, whole-body vibration and geographical region. Confounders are mutually adjusted and adjusted for standing-years.*

Men

An increased risk of THR for men with increasing ton-years and lifting-years was seen (table 8). The single most important risk factor was still BMI above 30. Self-reported exposures of heavy lifting showed an exposure-response relationship. The continuous variable showed a statistically significant association with THR, although lower than for the JEM assessed exposure.

Table 8.
Risk estimates of THR for men, estimated by conditional logistic regression (n=1955)

Exposure	Univariate OR	Adjusted# OR	95% CI
Standing-years (5 year increase)	1.01	1.00	0.95 - 1.05
Ton-years (5 year increase)	1.03	1.03	1.01 - 1.06
Lifting-years (5 year increase)	1.04	1.04	1.01 - 1.07
Smoking 5 pack-year	0.99	0.99	0.97 - 1.01
Earlier trauma	1.48	1.40	1.09 - 1.80
Familiar predisposition	1.79	1.64	1.09 - 2.46
Type of sport			
Endurance sport	1.13	1.05	0.79 - 1.39
Combination of endurance and risk sport	1.63	1.59	1.24 - 2.04
Contact/risk sport	1.34	1.35	1.05 - 1.73
Co-morbidity	0.86	0.77	0.54 - 1.10
BMI at 25			
<18.5	0.26	0.20	0.04 - 0.90
18.5 - <25	1.00	1.00	
25 - <30	1.32	1.30	1.04 - 1.63
30+	1.88	1.96	1.15 - 3.33
Self-reported lifting			
0 ton years	1.00	1.00	
1 - <10 ton years	1.22	1.08	0.71 – 1.65
10 - <50 ton years	1.46	1.42	1.09 – 1.85
50+ ton years	1.76	1.61	1.19 – 2.19
Ton-years (5 year increase)	1.02	1.01	1.00 – 1.02

 # Explanatory variables are adjusted for smoking, earlier fractures, familiar predisposition, type of sports, co-morbidity, BMI at 25, whole-body vibration, and geographical region.
Confounders are mutually adjusted and adjusted for standing-years.

For the total study population there seemed to be a tendency of a threshold when reaching 20 ton-years (figure 8). For women (figure 9a) there was, as expected, no sign of a threshold, and no even pattern of an exposure-response relationship. For men, there seemed to be an overall increasing risk until reaching 40 ton-years (figure 9b).

Figure 8.
Spline regression on ton-years for the total study population*
**Ton-years: number of years with lifting five tons per day*
● = *OR,* ▬ = *spline regression line*

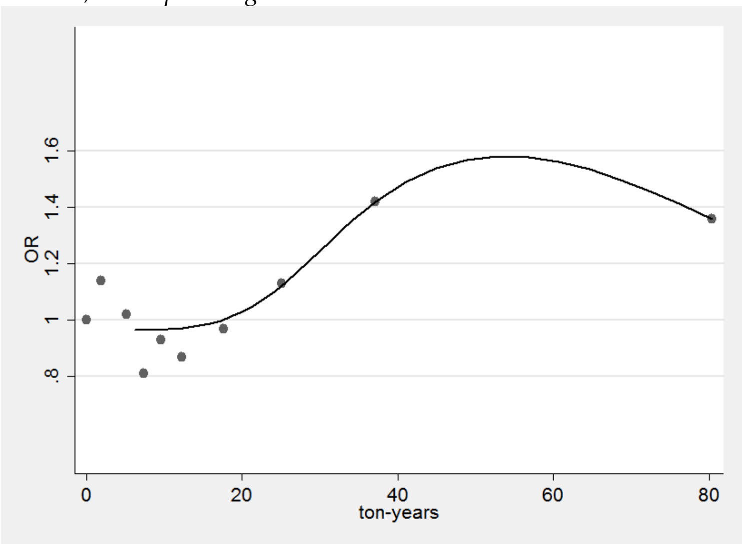
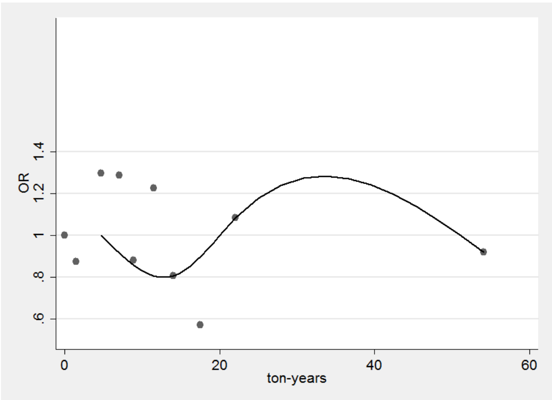
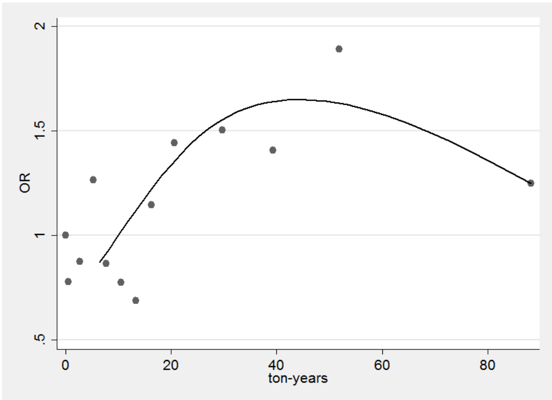


Figure 9.
Spline regression on ton-years for women and men.*
**Ton-years: number of years with lifting five tons per day*
♦=*OR,* ▬ = *Spline regression line*

a) Women



b) Men



8. Discussion

Key findings

An exposure-response relationship between cumulative physical exposures and THR was seen for men but not for women. For overall cumulative exposure, a threshold at 16-20 point-years was seen. Hence, a reason to investigate specific exposures in the work environment, have been established.

For men, heavy lifting, defined as ton-years or lifting-years showed a positive association with THR. For women no such relationships was found

When using the self-reported exposures, we did not see a higher risk of THR, than when using independent exposure assessment, neither for men, nor women.

Methodological issues

Study designs

Randomised clinical trials would be the best way to observe an exposure-response relationship between physical work loads and THR, since the amount of exposure is highly controlled, and other variables can be controlled as well. Nevertheless, it is not possible to assign individuals to different exposure levels over several years, as would be expected, when studying THR.

In order to establish an overview of the general working population, we conducted a register-based cohort study. In a cohort study, it can be difficult to study outcomes with a long latency. However, in the Danish system, with many national registers of high quality, it is possible to follow large cohorts of individuals, with complete follow-up, since information is kept in the registers, and not are to be obtained from the individuals directly. Hence, it is possible to create and carry out nationwide studies, and not just studies concentrating on specific industries or small populations. Cohort studies have the advantage of assessing exposure independently of outcome, hence enabling investigation of cause-effect (or exposure-response) relationships. Drawbacks are incomplete follow-up, which is not an issue in our study, where we can follow the whole population in national registers, and limited exposure and confounder information.

To achieve more detailed exposure and confounder information, we did a nested-case control study, within the cohort from paper II. Lately there have been some controversy about this design and the risk of exaggerating exposure-response relationships, due to unrecognized study design bias (97). But this have been refuted in several papers (94;98). Wacholder stating that a properly executed case-control study nested in a cohort is valid if the corresponding analysis of the cohort is valid (98). Case-control studies are primarily used when studying rare diseases. In this case, THR could be argued to be a "rare disease", since it takes a very long follow-up of a cohort, before a reasonable amount of cases arise to be useful in a cohort study. A second reason for our usage of the design, is efficient resource allocation to refining exposure assessment (99). It is simply not practically possible to assign individual exposure assessments to everyone in the entire Danish working population. And a third reason for choosing this design is the fact that Greenland and Thomas very early on showed that in the nested case-control design the odds-ratio very consistently estimates the incidence-density ratio which is very close to the risk ratio, especially with "true" risk ratios of five and below (95). A nested case-control study has the advantage of knowledge of the total population, from which cases and controls are sampled. Hence, we are certain that cases and controls arise from the same underlying population, and thus not a sample with very different background risk or exposure profile. It has also been reported that there are substantial savings, while still achieving the advantages of a cohort study, when conducting nested case-control studies (100).

Choice of outcome

When using THR as outcome, the question of economic ability is essential, since most health care systems are based on some self-financing by the patient. In Denmark everybody is covered by public health care and economic abilities does not play a role in deciding whether to undergo joint replacement surgery. Denmark is thus different from most other countries, where using THR as outcome, can be considered problematic due to differences in economic abilities among patients.

Total hip replacement is considered a surrogate measure for symptomatic end-stage OA (101), and thus the only way to ensure that OA is of substantial clinical importance. Many, who suffer from OA, never advance further in the health care system than their general practitioner, and thus are not retrievable in the national registers. Others have been given the diagnosis based on radiographic changes, without or with only very few clinical symptoms, which is not useful in a public health care perspective. In a public health perspective THR is a relevant choice of outcome, since the economic and social consequences are important. If the interest of the study were to see whether physical loads damaged cartilage, the choice of outcome would be radiographic changes, with or without clinical symptoms.

Exposure assessment

In order to avoid risk-assessment to be influenced by case-status the use of independent exposure assessment is crucial. Self-reported exposures tend to overestimate the risk. Thus, we developed exposure matrices for the two studies, in order to attain independent exposure assessment. The use of independent exposure assessments is a strength in our studies; this minimizes recall-bias and risk of inflation bias, if cases overestimate their exposure compared to controls.

The use of an IEM or JEM, yields misclassification (66;67). Subjects working within the same industry, do not all have the same occupational title, and those with same occupational title do not necessarily perform the same tasks. This misclassification might be the biggest drawback in our studies, where we used exposure matrixes. We expect this misclassification to be non-differential, yielding odd ratios closer to unity, hence underestimating the risk. Since we actually did find an association, at least for men, the use of an industry exposure matrix has not totally obscured relationships. The IEM and JEM were not gender specific. Maybe underestimation of risks was especially pronounced among women, because women in industries with high exposures may be more likely than men to hold jobs with minimal physical load, e.g. office jobs. A greater tendency towards exposure misclassification for females than for males may be part of the explanation why we found an exposure-response relationship for men, but not for women. Maybe more valid exposure estimates could have been obtained if our IEM had been made for women and men separately. But then again, the Danish labour market is to a large extent gender segregated so that men and women work in different jobs, which means that the practical significance of such an effort may be limited. This could explain why we did not find any association for women in the cohort study.

We have tried to minimize misclassification, when using the JEM, by constructing the HEGs. Since we actually did find a relationship, at least for men, when using the JEM to obtain exposure assessments, this can be accepted as stronger evidence towards a relationship between exposure and outcome, at least for men. It has been showed that women tend to use higher force when performing the same tasks as men (102). Hence, there is a risk of underestimating exposure for women in high exposure occupations, leading to smaller exposure contrast and risk estimates close to unity. This could explain our findings of no association between increasing exposure and THR for women in the case-control study.

The JEM covers 556 ISCO occupational titles, and can be used in studies of the general population. Since the exposures are assessed quantitatively, it is possible to investigate exposure-response relationships if present, and look for thresholds. Thresholds can only be established with quantitative measures of exposure, and thus the design of this JEM is a strength.

Selection bias

Selection bias arises when those included in the study are different from those not included concerning both exposure and outcome. A high participation rate is sought to reduce the risk of selection bias.

In the register-based cohort study, we used the benefits of the national Danish registers, and the unique personal number in the CRS to link information from several registers. This gives us the opportunity to study the whole working population, and not just concentrate on specific industries or companies. We do not expect selection bias to be of major concern, since we are able to follow the total population in registers, and thus have no loss to follow-up. This eliminates the risk of selection bias due to differential dropout of the study. Inclusion in the study could be hampered by selection bias, but this would be due to societal changes and the risk of unemployment in different time-periods, which we cannot account for. The sheer size of the cohort study is a strength, since it virtually comprises a full generation of working Danes.

In the case-control study, participation rates were fairly high for both cases (78%) and controls (72%). Fewer controls than cases participated, which is a limitation in the case-control study, if non-participation is related to exposure or outcome. We strived to present the questionnaire in a way not to reject cases, not emphasising neither outcome nor exposures, but aiming at a more broad focus of work and health in general. Non-participants could be compared to participants via the Danish Labour Market Supplementary Scheme, to see if non-participants differed on the industries in which they were employed, or had a difference in employment degree. If non-participants (mostly controls) were mainly employed in low exposure industries, our risk estimates would move towards unity.

Information bias

Self-reported information poses a risk of information bias, especially if cases tend to report differently from controls or the general population.

When linking information from the Danish Labour Market Supplementary Pension Scheme to the IEM, we used only independent information of exposure. If the industry coding in the Danish Labour Market Supplementary Pension Scheme is flawed this would lead to information bias. As far as we know, there have been no studies of the completeness of this register, but as reporting is mandatory, we expect a high degree of completeness of employed persons. Those who have been self-employed are not registered in this register. If a person have been self-employed for some periods, and employed somewhere else in other periods, the cumulative exposure will be underestimated, if self-employment has been in exposed industries.

We linked ISCO occupational titles to the JEM. It has been shown that recall of occupational titles appears to be reliable, even after a considerable number of years (49). Thus, the self-reported information on occupation used in this study, can be expected to be valid.

When studying BMI in a case-control study, participant's weight could be influenced by case-status, and it is a strength that we used BMI at the age of 25 in our study. It yielded an increase in missing information, but in the trade off between BMI before surgery and more information, BMI before surgery seems most important, if BMI are to be accepted as a risk factor. We used self-reported height and weight, which can be expected to differ from measured weight, but shown to be valid for identifying associations in epidemiological studies (103). Hence, the associations found in our study can be taken for valid, but the exact levels of BMI might differ from those attained from direct measurements.

Confounding

Confounding is a concern when doing a fully register-based study. We have no means of gathering information on dietary habits, physical activity outside work, smoking or alcohol consumption, etc. Our case-control study (paper III) showed that smoking did not confound risk estimates; hence, we do not expect it to confound the cohort study. But it has been shown that physical inactivity is associated with musculoskeletal complaints (104), and this might be of importance in a study of THR, since pain is one of the reasons why people undergo joint replacement surgery. We could not control for this in the cohort study.

In the questionnaire, we asked for potential confounders. Not all confounders are known, and thus we have not been able to control for all confounders. This is not special in a study of THR, but a well-known phenomenon for all studies. It is not possible to rule out that unknown confounders influence the results for women. Thus, our two studies compliment each other.

Risk estimates are seen to reach a plateau after approximately 40 point years for men in the cohort study (paper II). This could be sue to healthy worker selection, where those who keep working in exposed industries might be those, who are more resistant towards physical exposures. In the case-control study, this is a possibility, as well.

Body mass index does not influence risk estimates greatly, especially for women in the case-control study (paper III). Our cohort study (paper II) could be confounded by BMI, but since the impact are small, we do not expect this to be a major confounder. Our findings, when looking at BMI as explanatory variable, are different from earlier findings. We found that women in the highest BMI group, had an increased risk of 5.69, almost three times as high as for men (1.96), where others report that BMI has higher impact in men than in women (5;74;105;106).

Socioeconomic status influenced the risk estimates in the cohort study (paper II), reducing these. A correlation between SES and exposure could result in over-controlling and risk estimates closer to unity. For women, a lower SES seemed to protect against THR. This could be explained, if women were categorised according to their husbands, and thus wife of farmers and those with small businesses, would end in the highest SES group. It can be expected that spouses of self-employed in farming or small businesses have worked a considerable amount of time in their husbands' farm or company, thus cumulating a high exposure.

Other methodological issues

Studying relationships between occupational exposures and physical symptoms or diseases raises a problem of distinguishing between symptoms being aggravated by exposure or exposure actually causing the disease. When calculating cumulative exposure in the case-control study, we aimed at addressing this issue. By disregarding the exposures during the last two years leading up to surgery, we wanted to diminish the risk that a high exposure in the years just before receiving THR would influence the likelihood of being referred for surgery due to symptom aggravation by exposure. In the cohort study, a similar approach could have been applied, but we, a priori, had decided on using the full cumulative work-life exposure. In addition, with up to 11 years of follow-up for non-cases the question of when to censor exposure is essential. Another way to investigate this relationship could be, to include the industry of employment the year of receiving THR in the analysis.

The question of gender seems to be important. A resent publication by Messing (96) addressed this problem. In the cohort study, we decided, from the beginning to analyse women and men independently. The case-control study was planned to analyse women and men in the same analysis, as we have reported. We also did the analysis as gender specific, hence minimizing the power of the study. This leads to larger confidence intervals, but cannot explain our findings of unity for women.

Comparison with relevant findings from other studies

Overall, our findings are in accordance with earlier studies, were relationships were seen between physical exposures at work and hip OA (differing definitions), for men. Findings for women are somewhat more mixed. In the following, previous studies concerning the risk of THR in relationship to occupational exposures are described.

Women

Compared to the study by Vingård (39), we did not find any increased risk of THR for women with any of the occupational exposures. Vingård found a statistically significant increased risk for jumps between different levels, number of flight climbed, and years with non-occupational physical demanding tasks. They found a non-significant increased risk for standing/walking and heavy lifting, which we cannot show in our study, neither when using the JEM for exposure assessment nor for self-reported exposures. Cumulative exposure was used in this study, based on self-reported exposures, which could have led to inflated risk estimates, due to recall-bias. Flugsrud (11) reported an increased risk for women working in the most intensive group, a finding we can not retrieve in our data, neither in the cohort, nor in the case-control study. They used self-reported activity the year before being screened in a different study (of cardiovascular diseases) thus recall-bias does not seem to be a major problem. But another problem can be the time-period from exposure assessment to start of follow-up, some participants exposure have been assessed immediately before start of follow-up, others' 10 years before.

In the Japanese study by Yoshimura (28), it was not possible to differentiate between men and women, when looking at the results. The majority of cases were women (103 women vs. 11 men), and hence results are interpreted to be applicable to women. Here it was seen that lifting more than 50 kg more than once a week in main job, yielded an increased risk of four, and lifting more than 25 kg in the first job increased the risk 3.6 times. Again, exposure was based on self-reported exposures, and re-call bias might have influenced the risk estimates.

Men

Results from our register-based cohort study are in agreement with the cohort study by Flugsrud (11). He reported "physical activity at work" on a three level basis, and found an increased risk of 2.0 in the highest exposure group. Our result for the highest group was 1.33. As stated above, recall-bias does not seem to be a major problem, but the time-period from exposure assessment to start of follow-up, differ substantially between participants.

Concerning heavy lifting our finding support earlier findings by Vingård (38), Croft (17), Coggon (27), and Lau (12), who all found an exposure-response relationship between heavy lifting and the risk of OA. Only of these studies used cumulative exposure (38), and our risk estimates are again lower than those presented in the above mentioned studies.

The studies by Thelin (37), Tüchsen (35), and Järvholm (34), investigated occupational titles. The study by Järvholm could not establish statistically significant increased risk of THR for construction workers of various kinds compared to white-collar workers. The two other studies (35;37) are interpretable as those in heavy jobs have higher risks, also with increasing time spent in heavy jobs. Again, our findings corroborate to the evidence of increasing exposure to physical work loads yields increasing risk of THR for men.

The fact that our studies in general present lower risk estimates than earlier studies of THR, can, in part, be contributed to the use of exposure matrices. This, on the other hand, lends even bigger evidence towards a relationship between occupational exposure and the risk of THR for men.

Generalizability

Since our studies are based in the general working population, and not in an industry- or company-based setting, it is possible to generalize our findings to the working population in other countries with labour markets similar to the Danish. In Denmark, we have no mining industry, and thus this rather strenuous industry is not included in our studies at all. On the other hand, we expect the results to be of use in most of the Western World, where many of the most prevalent occupations are of similar nature.

9. Conclusion

Our hypothesis of increased cumulative physical work loads as a risk factor for primary OA leading to THR was accepted for men, but could not be corroborated for women.
This thesis are in agreement with earlier studies showing an increased risk of primary OA (defined in different ways) and increasing loads in the work environment for men. Risk estimates were somewhat lower than in other studies.

For men, our studies shows, an exposure-response relationship between working in industries with a high amount of combined physical exposure towards the lower extremities and the risk of receiving THR due to primary OA. This was also seen for heavy lifting, when looking into specific exposures in the work environment. For men an increased risk of 15% was seen after lifting more than five tons per day in five years.
A threshold for combined physical exposures, for men, when reaching 16-20 point-years was seen. From there the risk of THR rose until reaching 40 point-years, where the risk did not increase further.

For women no such associations were found. Neither for overall increasing exposure nor specific exposures.

Our findings, when using exposure matrices, add to the evidence of a relationship between occupational exposures and the risk of THR for men.

10. Perspectives and future research

The job exposure matrix was not developed as a fixed entity, and as such, it is under continually development. One possibility, for improving, could be the inclusion of direct measurements of exposures. It would also be of interest to see how it performs in other studies, e.g. in countries with a similar labour market compared to the Danish labour market. The JEM could also be used to study other outcomes, where physical exposures towards the lower extremities or heavy lifting are of interest, e.g. pregnancy outcomes, or inguinal hernias.

We still have no solid evidence of a JEM being the best way of assessing exposures in general population studies.

Even though we have found an exposure-response relationship between heavy lifting and the risk of primary OA leading to THR for men, we did not see it for women. This leads to the next question, of what makes women different from men. We do not expect the difference in amount of exposure to be the only issue.

On another level, the question of returning to work after joint replacement surgery is of importance too. A future study could be a follow-up of the cohort. In Denmark the DREAM register is a possibility to follow everybody to investigate whether a person is employed, on sick leave (more than two weeks continually), unemployed, or has taken early retirement (not old age pension or pension benefits before normal retirement pension). Here it would be of interest to see if those with high cumulative exposure are more prone to early retirement than those with low cumulative exposure.

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Appendices

A. Previous studies

Table 1A.
*Overview of methods used for physical exposure assessment in studies of primary osteoarthritis (several definitions), entailing information of study design. THR - Total hip replacement. * study of disability pension due to musculoskeletal disorders, † study of hip pain*

	Outcome assessment				
	THR	Waiting list THR	Radiographic	Clinical	Other*
Exposure assessment					
Occupational title – self-reported	Thelin 1999(37) Case-control		Jacobsson 1987 (19) Case-control	Rossignol 2005 (26) Cross-sectional	
Occupational title – register-based	Tüchsen 2003 (35) Cohort Järvholm 2008 (34) Cohort		Axmacher 1993 (15) Cohort		
Occupational title + expert assessment into broad categories	Vingård 1991 (36) Cohort Järvholm 2004 (33) Cohort				Vingård 1992 (41) Cohort *
Self-reported exposures	Vingård 1991 (38) Case-control Olsen 1994 (105) Case-control Vingård 1997 (39) Case-control Flugsrud 2002 (11) Cohort	Coggon 1998 (27) Case-control Yoshimura 2000 (28) Case-control Lau 2000 (12) Case-control	Typpö 1985 (106) Case-control Croft 1992 (17) Case-control Croft 1992 (16) Cross-sectional Roach 1994 (20) Case-control Thelin 1997 (21) Case-control Jacobsen 2004 (18) Cross-sectional Thelin 2004 (22) Case-control	Heliövaara (24) Cross-sectional Cvijetic 1999 (23) Cross-sectional Juhakoski 2009 (25) Cohort	Tüchsen 2003 (40) Cohort †
Expert assessment					
Job exposure matrix					
Direct observation					
Technical measurements					

Table 2A.
Chronological overview of studies concentration on occupational exposures and primary hip OA (defined in different ways)
THR - Total hip replacement, OA - osteoarthritis F - females, M - males, NA - not available, SHR - Standardised hospitalisation ratio

Year	Author	Exposure	Outcome	Population	Results / OR (95%)	Dose-response relationship	Comments
1985	Typpo(106)	Self-reported occupation and quality of work (mental, light manual, medium manual, heavy manual)	Radiographic OA	224 F cases 171 M cases	Subjects with heavy manual work constitute a relatively bigger part of cases, than mental workers. Among manual workers, farmers constitute the biggest group	NA	Qualitative exposure assessment
1987	Jacobsson(19)	Self-reported occupation (farming, forestry, industrial work = heavy labour)	Radiographic or waiting for THR	85 M waiting list 106 M Radiographic OA	Increased frequency of heavy labour, farming and heavy lifting among patients with hip OA	NA	Small study, Broad exposure category
1990	Thelin(37)	Self-reported occupational history	THR	105 M cases 222 M controls	3.2 (1.8 – 5.5) with more than 10 years of farming Years in farming 1-10: 2.1 (1.1. – 4.3) 11-20: 4.6 (2.0 – 11.0) 21-30: 2.5 (0.9 – 6.9) >30: 2.9 (1.6 – 5.5)	NO	Small study, Using job-titles only
1991	Vingård(38)	Self-reported job title, and specific exposures (calculated low, medium, high exposure using self-reported exposures)	THR	233 M cases 302 M controls	Static + dynamic Medium: 2.25 (1.35 – 3.76) High: 2.87 (1.79 – 4.62) Lifted tons Medium: 1.58 (0.93 – 2.66) High: 1.84 (1.12 – 3.03) Number of lift > 40 kg Medium: 1.38 (0.81 – 2.36) High: 2.40 (1.50 – 3.83)	YES, for increasing exposure	Aggregated exposure until the age of 49 Self-reported exposures,

Year	*Author*	*Exposure*	*Outcome*	*Population*	*Results / OR (95%)*	*Dose-response relationship*	*Comments*
1991	Vingård(36)	Self-reported job title in blue-collar jobs. Expert assessment into light or heavy work	Hospitalized with hip OA	221 F cases 1244 M cases	Born 1905 – 1924 Women: 1.6 (0.9 – 3.1) Men: 2.2 (1.6 – 2.8) Born 1925 – 1945 Women: 1.1 (0.9 – 1.5) Men: 2.0 (1.6 – 2.3)	NA	Qualitative exposure assessment based on job-titles
1992	Vingård(41)	Self-reported occupational history. Expert assessment into low, medium, or high exposure	Disability pension due to diagnosed hip OA	140 M cases 298 M controls	Medium: 4.1 (2.4 – 7.1) High: 12.4 (6.7 – 23.0)	YES, for increasing exposure	Qualitative exposure assessment based on job-titles
1992	Croft(17)	Self-reported specific physical activities	Radiographic OA	245 M cases 294 M controls	Lifting > 56 lbs by hand (severe cases – 49 men) 1-19 years: 1.2 (0.5 – 2.9) ≥20 years: 2.5 (1.1 – 5.7) Standing > 2 hours/day (severe cases – 51 men) 20-39 years: 1.5 (0.5 – 4.8) ≥40 years: 2.7 (1.0 – 7.3)	YES, for increasing amount of years with exposure	Quantitative exposure assessment based on self-report, X-ray not due to arthritis
1992	Croft(16)	Self-reported job titles and specific tasks within farming	Radiographic OA	167 M farmers 83 M controls	Duration of farming 1-9 years: 4.5 (0.8 – 26.3) ≥10 years: 9.3 (1.9 – 44.5)	YES, increasing time spent in farming	Small study, Farmers only, Qualitative exposure assessment
1993	Heliövaara(24)	Questionnaire, self-reported physical exposures → sum index of physical stress at work	Clinical OA	7217 persons 137 M cases 232 F cases	Sum index 1: 1.2 (0.9 – 1.8) 2: 1.9 (1.4 – 2.6) 3: 2.7 (1.8 – 3.9) 4-5: 2.7 (1.7 – 4.4)	YES, with increasing sum index	Men and women could not be distinguished in results, Sum-index = qualitative exposure assessment

Year	*Author*	*Exposure*	*Outcome*	*Population*	*Results / OR (95%)*	*Dose-response relationship*	*Comments*
1993	Axmacher(15)	Occupation Farmer vs. general population	Radiographic OA (colon- & urography)	565 M farmers 1250 M city-dwellers	A much higher percentage of the farming population reported primary hip OA than among the general population	NA	Qualitative exposure assessment
1994	Roach(20)	Self-reported occupational categories, leading to three levels (light, intermediate, heavy)	Radiographic OA	99 M cases 233 M controls	Intermediate: 1.9 (1.0 – 3.8) High: 2.4 (1.3 – 4.3)	YES, for increasing exposure	Small study. Controls with different disease status, Qualitative exposure assessment
1994	Olsen(105)	Self-reported job title, and specific exposures (calculated low, medium, high exposure using self-reported exposures)	THR	239 M cases 302 M controls	Etiologic fraction Static + dynamic Low: 0.16 Medium: 0.29 High: 0.44	NA	Aggregated exposure until the age of 49 Self-reported exposures, Qualitative exposure assessment
1997	Thelin(21)	Self-reported previous occupations and specific physical activities as farmer	Radiographic OA	216 M cases 479 M controls	Farming 1-10 years: 1.63 (1.03 – 2.60) 11-20 years: 1.67 (0.87 – 3.23) 21-30 years: 4.20 (1.97 – 8.97) >30 years: 4.45 (2.90 – 6.83)	YES, for increasing time spent in farming	Qualitative exposure assessment,. Few subjects in the different exposure groups

Year	*Author*	*Exposure*	*Outcome*	*Population*	*Results / OR (95%)*	*Dose-response relationship*	*Comments*
1997	Vingård(39)	Self-reported occupational history, and specific physical activities. Aggregated exposure was calculated and three levels were created (low, medium, high exposure)	THR	230 F cases 273 F controls	Standing Medium: 1.4 (0.8 – 2.2) High: 1.6 (0.9 – 2.8) Heavy lifts Medium: 1.1 (0.7 – 1.7) High: 1.5 (0.9 – 2.5)	YES, for increasing exposure to standing and heavy lifting	Aggregated exposure age 16-50, Self-reported exposures, Qualitative exposure assessment
1998	Coggon(27)	Self-reported occupational history, and specific physical activities	Waiting list for THR	210 M cases 401 F cases	<u>Standing > 2 hours/day</u> 0.1 – 9.9 years Men: 0.2 (0.0 – 1.4) Women: 1.1 (0.6 – 2.0) 10.0-19.9 years Men: 0.4 (0.1 – 2.4) Women: 1.1 (0.6 – 1.9) ≥20 years Men: 0.5 (0.1 – 2.3) Women: 1.3 (0.7 – 2.1) <u>Lifting > 25 kg, up to 10 years before entry into study</u> 0.1 – 9.9 years Men: 0.8 (0.4 – 1.7) Women: 1.1 (0.6 – 1.7) 10.0-19.9 years Men: 1.5 (0.6 – 3.8) Women: 1.4 (0.7 – 2.9) ≥20 years Men: 2.3 (1.3 – 4.4) Women: 0.8 (0.4 – 1.5)	YES, for heavy lifting for men. A tendency was seen for standing for both men and women.	Self-reported exposure for each job held more than one year

Year	*Author*	*Exposure*	*Outcome*	*Population*	*Results / OR (95%)*	*Dose-response relationship*	*Comments*
1999	Cvitetic(23)	Self-reported physical activity in four categories (cat1 mostly sedentary, cat2 > 80% of time standing, cat3 >80% of time non-sitting and light lifting, cat4 >805 of time non-sitting and lifting >5 kg)	Clinical and radiographic OA	292 F 298 M	Radiologic signs Men: (Cat1 as reference) Cat2: 1.50 (0.60 – 3.21) Cat3: 1.16 (0.28 – 2.30) Cat4: 1.15 (0.52 – 2.52) Women: (Cat1 as reference) Cat2: 1.45 (0.49 – 3.58) Cat3: 1.19 (0.65 – 2.32) Cat4: 1.34 (0.52 – 3.04)	NO	Not possible to rank the four categories considering exposure levels
2000	Yoshimura(28)	Self-reported physical activities	Waiting list for THR	103 F cases 11 M cases	Main job lifting 10+ kg: 1.2 (0.6 – 2.1) 25+ kg: 1.5 (0.7 – 3.0) 50+ kg: 4.1 (1.1 – 15.2)	YES, with increasing exposure to heavy lifting	Small study, Japanese population, Very few men
2000	Lau(12)	Self-reported physical activities in reported main job	THR, waiting list for THR, radiographic OA	108 F cases 30 M cases	<u>Lifting 10 kg or more</u> 1-10 times/week Men: 1.9 (0.6 – 6.6) Women: 0.7 (0.4 – 1.5) >10 times/week Men: 5.3 (1.8 – 15.8) Women: 3.0 (1.8 – 5.1) <u>Lifting 50 kg or more</u> 1-10 times/week Men: 8.5 (1.6 – 45.3) Women: 2.0 (0.9 – 4.6) >10 times/week Men: 9.6 (2.2 – 42.2) Women: 2.9 (1.5 – 5.6) <u>Walking <2 hours/day</u> Men: 3.9 (1.3 – 12.1) Women: 1.4 (0.9 – 2.3)	YES, for increasing exposure to heavy lifting NA for walking	Small study, Chinese population, Very few men, Difference in exposure assessment between cases and controls

Year	*Author*	*Exposure*	*Outcome*	*Population*	*Results / OR (95%)*	*Dose-response relationship*	*Comments*
2002	Flugsrud(11)	Self-reported level of activity at work during the last year (sedentary, moderate, intermediate, intensive)	THR	50,034 persons 382 F / 268 M cases	Physical activity at work Men: Moderate: 1.5 (1.0 – 2.2) Intermediate: 1.7 (1.1 – 2.4) Intensive: 2.0 (1.5 – 3.0) Women: Moderate: 1.1 (0.8 – 1.6) Intermediate: 1.4 (0.9 – 2.0) Intensive: 2.1 (1.3 – 3.3)	YES, with increasing exposure	Nine years of follow-up, Activity the year before start of follow-up, Few cases, Qualitative exposure assessment
2003	Tüchsen(35)	Register-based, occupational title	Hospitalised with hip OA	Approximately 1 million M	1994 – 1999 (SHR) Farmers: 286 (262 – 313) Wood product machine operators: 205 (119 – 328) Machine operators and assemblers: 207 (118 – 336)	NA	Several cohorts, Five years follow-up, Job-title the year before start of follow-up
2003	Tüchsen(40)	Sself-reported physical exposures	Hip pain	2030 M /132 cases 1684 F / 91 cases	Physical demanding work ≥25% of work hours: 1.83 (1.23 – 2.71) Heavy lifting ≥25% of work hours: 1.08 (0.72 – 1.63)	NA	Few cases, Young population, Difficult to distinguish between men and women
2004	Jacobsen(18)	Self-reported physical activities (lifting)	Radiographic OA (JSW)	1018 M 1554 F	Results reported as mean Joint space width (JSW) in different categories of heavy lifting. No association between heavy lifting and JSW	NA	Radiographs on all participants, Non-symptomatic subjects

Year	*Author*	*Exposure*	*Outcome*	*Population*	*Results / OR (95%)*	*Dose-response relationship*	*Comments*
2004	Järvholm(33)	Register-based job titles, whole body vibration estimated by occupational hygienist (high/low)	THR	5643 exposed and 64225 non-exposed All males	Whole-body vibration 0.84 (0.53 – 1.28) Compared with painters and electricians	NA	Dichotomous exposure assessment
2004	Thelin(22)	Self-reportedwork tasks as farmer	Radiographic OA	369 M cases (farmers) 369 M controls (farmers)	Different tasks in farm work Dairy >40 cows: 1.4 (1.09 – 1.86) Swine confinement, sows: 1.2 (1.02 – 1.60) Cattle >50 heads: 1.0 (0.49 – 1.91) Crop rising >100 ha farm land: 0.7 (0.59 – 0.95)	NA	Only farmers
2005	Rossignol(26)	Self-reported occupational titles	Clinically diagnosed OA	1615 M / 572 cases 1219 F / 329 cases	Results presented as (observed cases/expected cases) for different occupations Self-employed in different manual and food sectors: 2.9 (2.6 – 3.3) Agriculture: 2.8 (2.5 – 3.2)	NA	Qualitative exposure assessment
2008	Järvholm(34)	Register-based occupational title	Diagnosed hip OA or THR	204741 M 1260 cases	Compared to white-collar workers Floor layers 1.58 (0.93 – 2.68) Asphalt workers 1.50 (0.9 – 2.49) Rock workers 1.37 (0.87 – 2.13)	NA	Long follow-up, Qualitative exposure assessment

Year	*Author*	*Exposure*	*Outcome*	*Population*	*Results / OR (95%)*	*Dose-response relationship*	*Comments*
2009	Juhakoski(25)	Self-reported physical work load in six levels (light sedentary, other sedentary, light standing, fairly light/medium heavy, heavy manual, very heavy manual)	Clinical OA	356 M / 17 cases 523 F / 24 cases	Adjusted for all covariates Other sedentary: 1.1 (0.1 – 10.0) Light standing: 1.2 (0.4 – 3.4) Fairly light: 3.1 (1.2 – 8.0) Heavy manual: 6.7 (2.3 – 19.5) Very heavy – none	YES, with increasing exposure	Qualitative exposure assessment, Few cases

B. Questionnaire (in Danish)

Videnskabelig undersøgelse af
Arbejde, Led og Sundhed i Danmark

Århus Universitetshospital
Århus Sygehus
Arbejdsmedicinsk Klinik

VEJLEDNING

Du bedes besvare spørgsmålene i den opstillede rækkefølge. Giv dig god tid til at læse spørgsmålene og de vejledninger, der er undervejs.

Det er naturligt, at du kan være i tvivl ved nogle af spørgsmålene, men det er vigtigt, du svarer, så godt du kan alligevel, og at alle spørgsmålene besvares.

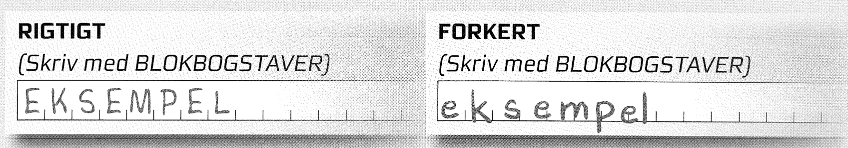
Inden for 3 uger vil du få en påmindelse om undersøgelsen, og hvis vi efter yderligere ca. 4 uger ikke har modtaget dit svar, sender vi et nyt spørgeskema. Dette gøres for at undgå manglende besvarelser, som skyldes ren forglemmelse eller almindelig travlhed i hverdagen.

På side 11 i spørgeskemaet har du mulighed for at skrive kommentarer.

Har du spørgsmål i forbindelse med undersøgelsen, er du velkommen til at kontakte Tine Steen Rubak på tlf. 2758 4296 på hverdage mellem kl. 9.00 og 15.00 eller via e-mail: truba@as.aaa.dk

SÅDAN UDFYLDER DU SPØRGESKEMAET

Brug venligst en **sort** eller **blå kuglepen** eller **tynd** filtpen.
Svarene bliver skannet ind på en maskine, så alle tal, bogstaver og kryds skal være nemme at tolke, som vist i nedenstående eksempler.



Sæt tydelige kryds X

Hvis et felt er **udfyldt forkert**, skraveres den pågældende kasse og krydset sættes i den rigtige.

Tallene skrives i felterne.

Tallene rettes ved helt at overstrege det forkerte tal og skrive det rigtige ovenover.

UDDANNELSE OG ARBEJDE

1 Hvilken erhvervsmæssig uddannelse har du?

(Sæt X ved den længste uddannelse du har fuldført)

- Ingen (ufaglært) ☐
- Et eller flere kortere kurser (specialarbejderkurser, arbejdsmarkedskurser m.v.) ☐
- Faglært inden for håndværk, handel, kontor ☐
- Kort videregående uddannelse, under 3 år (fx social- og sundhedshjælper eller -assistent, pædagogisk grunduddannelse) ☐
- Mellemlang videregående uddannelse, 3-4 år (fx skolelærer, pædagog, sygeplejerske) ☐
- Lang videregående uddannelse, over 4 år (fx økonom, jurist, læge, psykolog) ☐
- Anden uddannelse ☐

Hvilken anden uddannelse? (Skriv med BLOKBOGSTAVER)

2 Hvornår startede du på arbejdsmarkedet?

Skriv årstal: ____ *(Se bort fra studie- og fritidsjob)*

De næste spørgsmål handler om din hovedbeskæftigelse i bestemte perioder.
Spørgsmålene for hver periode er de samme.
Det er vigtigt, at du besvarer spørgsmålene for alle perioder, hvor du var i arbejde.

Med hovedbeskæftigelse menes den job-type eller det fag, du havde i længst tid.

Vær så præcis som muligt: skriv fx »murer« i stedet for »håndværker« eller »pakker på møbelfabrik« i stedet for »pakker«.

Spørgsmålene starter tættest på i dag og går bagud i tiden.
Hvis du ikke var i arbejde i en periode, bedes du angive dette.

3

a **Var du i arbejde i 8-års perioden 2000-2007?**

Nej ☐ *Gå til spørgsmål 4*
Ja ☐ *Besvar nedenstående spørgsmål*

b **Hvor mange år var du i arbejde?**

Skriv antal år: ☐

c **Hvad var din hovedbeskæftigelse?**

(Skriv den danske stillingsbetegnelse med BLOKBOGSTAVER. Hvis du havde flere jobs af lige lang varighed, bedes du skrive det første af disse)

4

a **Var du i arbejde i 10-års perioden 1990-1999?**

Nej ☐ *Gå til spørgsmål 5*
Ja ☐ *Besvar nedenstående spørgsmål*

b **Hvor mange år var du i arbejde?**

Skriv antal år: ☐

c **Var det samme hovedbeskæftigelse som i spørgsmål 3?**

Ja ☐ *Gå til spørgsmål 5*
Nej ☐ *Besvar nedenstående spørgsmål*

Hvad var din hovedbeskæftigelse?
(Skriv den danske stillingsbetegnelse med BLOKBOGSTAVER. Hvis du havde flere jobs af lige lang varighed, bedes du skrive det første af disse)

5

a **Var du i arbejde i 10-års perioden 1980-1989?**

Nej ☐ *Gå til spørgsmål 6*

Ja ☐ *Besvar nedenstående spørgsmål*

b **Hvor mange år var du i arbejde?**

Skriv antal år: ☐

c **Var det samme hovedbeskæftigelse som i spørgsmål 4?**

Ja ☐ *Gå til spørgsmål 6*

Nej ☐ *Besvar nedenstående spørgsmål*

Hvad var din hovedbeskæftigelse?
(Skriv den danske stillingsbetegnelse med BLOKBOGSTAVER. Hvis du havde flere jobs af lige lang varighed, bedes du skrive det første af disse)

6 **Hvilken hovedbeskæftigelse har du samlet set haft i længst tid efter 1980?**

(Skriv den danske stillingsbetegnelse med BLOKBOGSTAVER)

Spørgsmål 7 - 9 handler om den hovedbeskæftigelse, du angav i spørgsmål 6.

7 **Medførte dit arbejde i denne hovedbeskæftigelse, at du i løbet af en typisk arbejdsdag ...** *(Sæt ét X i hver linje)*

	Nej	Ja, mindre end ½ time	Ja, ½ til 2 timer	Ja, 2 til 4 timer	Ja, 4 timer eller mere
a kørte/betjente landbrugsmaskiner, entreprenørmaskiner eller bæltekøretøjer?	☐	☐	☐	☐	☐
b arbejdede i knæliggende eller hugsiddende stillinger?	☐	☐	☐	☐	☐
c arbejdede i stående eller gående stillinger?	☐	☐	☐	☐	☐
d arbejdede i siddende stilling?	☐	☐	☐	☐	☐

8 Medførte dit arbejde i denne hovedbeskæftigelse, at du i løbet af en typisk arbejdsdag med ret ryg…

(Sæt ét X i hver linje)

	Nej	1-10 gange om dagen	11-100 gange om dagen	Over 100 gange om dagen
a bar/løftede byrder, der vejede mindre end 10 kg?	☐	☐	☐	☐
b bar/løftede byrder, der vejede 10-20 kg?	☐	☐	☐	☐
c bar/løftede byrder, der vejede over 20 kg?	☐	☐	☐	☐

9 Medførte dit arbejde i denne hovedbeskæftigelse, at du i løbet af en typisk arbejdsdag med foroverbøjet ryg…

(Sæt ét X i hver linje)

	Nej	1-10 gange om dagen	11-100 gange om dagen	Over 100 gange om dagen
a bar/løftede byrder, der vejede mindre end 10 kg?	☐	☐	☐	☐
b bar/løftede byrder, der vejede 10-20 kg?	☐	☐	☐	☐
c bar/løftede byrder, der vejede over 20 kg?	☐	☐	☐	☐

10 Var du i arbejde før 1980?

Nej ☐ *Gå til spørgsmål 11*

Ja ☐ *Besvar nedenstående spørgsmål*

Hvilken hovedbeskæftigelse har du haft i længst tid før 1980?
(Skriv den danske stillingsbetegnelse med BLOKBOGSTAVER)

HELBRED

11 Hvor meget har du inden for de <u>seneste 12 måneder</u> været generet af smerter eller ubehag i ... *(Sæt ét X i hver linje)*

	Slet ikke	Meget lidt	Lidt	Noget	En hel del	Meget	Særdeles meget
a nakke og/eller skuldre?	☐	☐	☐	☐	☐	☐	☐
b albuer, underarme og/eller hænder?	☐	☐	☐	☐	☐	☐	☐
c lænderyggen?	☐	☐	☐	☐	☐	☐	☐
d hofter?	☐	☐	☐	☐	☐	☐	☐
e knæ?	☐	☐	☐	☐	☐	☐	☐
f ankler og fodled?	☐	☐	☐	☐	☐	☐	☐

12 Har du nogen sinde haft brud på... *(Sæt ét X i hver linje)*

a bækken?	Nej ☐	Ja ☐	skriv årstal ca: ☐☐☐☐
b hofte?	Nej ☐	Ja ☐	skriv årstal ca: ☐☐☐☐
c lårben?	Nej ☐	Ja ☐	skriv årstal ca: ☐☐☐☐
d knæ?	Nej ☐	Ja ☐	skriv årstal ca: ☐☐☐☐
e underben?	Nej ☐	Ja ☐	skriv årstal ca: ☐☐☐☐
f ankel?	Nej ☐	Ja ☐	skriv årstal ca: ☐☐☐☐

13 Har du nogensinde beskadiget, eller er du blevet opereret i et eller begge knæ?

Nej ☐ *Gå til spørgsmål 14*

Ja ☐ Skriv årstal ca: ☐☐☐☐

(Hvis du er opereret flere gange, skriv årstal for første operation.)

14 Har du de sidste 48 timer haft smerter, stivhed eller andet besvær i din(e) hofte(r)?

(Ved stivhed forstås fornemmelsen af at have nedsat bevægelighed i leddet.)

Nej ☐ *Gå til spørgsmål 20, side 7*

Ja ☐ *Besvar nedenstående spørgsmål*

15 Hvilken hofte har generet dig mest de sidste 48 timer?

Højre ☐

Venstre ☐

Begge lige meget ☐

I det følgende beder vi dig besvare en række spørgsmål om smerter, stivhed i led og besvær med at udføre dagligdags opgaver.

Tænk på smerterne, du har i den hofte, der har generet dig mest de sidste 48 timer.

16 Hvor mange smerter har du,... *(Sæt ét X i hver linje)*

	Ingen smerter	Lette smerter	Moderate smerter	Svære smerter	Ekstreme smerter
a når du går på jævnt underlag?	☐	☐	☐	☐	☐
b når du går op eller ned ad trapper?	☐	☐	☐	☐	☐
c om natten, når du ligger i sengen?	☐	☐	☐	☐	☐
d når du sidder eller ligger?	☐	☐	☐	☐	☐
e når du står oprejst?	☐	☐	☐	☐	☐

Tænk på stivheden (ikke smerterne), du har i den hofte, der har generet dig mest de sidste 48 timer. Ved stivhed forstås fornemmelsen af at have nedsat bevægelighed i leddet.

17 Hvor alvorlig er stivheden, når du vågner om morgenen?

	Ingen stivhed	Let stivhed	Moderat stivhed	Svær stivhed	Ekstrem stivhed
(Sæt ét X)	☐	☐	☐	☐	☐

18 Hvor alvorlig er stivheden, når du har siddet, ligget eller hvilet dig senere på dagen?

	Ingen stivhed	Let stivhed	Moderat stivhed	Svær stivhed	Ekstrem stivhed
(Sæt ét X)	☐	☐	☐	☐	☐

Tænk på hvor vanskeligt det har været for dig at udføre daglige aktiviteter i de sidste 48 timer på grund af problemer med den hofte, der har generet mest.

19 Hvor vanskeligt er det for dig at... *(Sæt ét X i hver linje)*

	Slet ikke vanskeligt	Lidt vanske-ligt	Moderat vanske-ligt	Meget vanske-ligt	Ekstremt vanske-ligt
a gå op ad trapper?	☐	☐	☐	☐	☐
b rejse dig op efter at have siddet?	☐	☐	☐	☐	☐
c gå på jævnt underlag?	☐	☐	☐	☐	☐
d stige ind i/ud af en bil eller på/af en bus?	☐	☐	☐	☐	☐
e tage sokker/strømper på?	☐	☐	☐	☐	☐
f stå op af sengen?	☐	☐	☐	☐	☐
g sidde?	☐	☐	☐	☐	☐

20 Hvordan synes du, dit helbred er alt i alt?

	Frem-ragende	Vældig godt	Godt	Mindre godt	Dårligt
(Sæt ét X)	☐	☐	☐	☐	☐

21 Hvor stor en del af tiden i de sidste 4 uger har du... *(Sæt ét X i hver linje)*

	Hele tiden	Det meste af tiden	En hel del af tiden	Noget af tiden	Lidt af tiden	På intet tids-punkt
a følt dig veloplagt og fuld af liv?	☐	☐	☐	☐	☐	☐
b været meget nervøs?	☐	☐	☐	☐	☐	☐
c været så langt nede, at intet kunne muntre dig op?	☐	☐	☐	☐	☐	☐
d følt dig rolig og afslappet?	☐	☐	☐	☐	☐	☐
e været fuld af energi?	☐	☐	☐	☐	☐	☐
f følt dig trist til mode?	☐	☐	☐	☐	☐	☐
g følt dig udslidt?	☐	☐	☐	☐	☐	☐
h været glad og tilfreds?	☐	☐	☐	☐	☐	☐
i følt dig træt?	☐	☐	☐	☐	☐	☐

22 Har du nogensinde fået behandling med kønshormon?

(fx p-piller, p-sprøjte, østrogen i forbindelse med overgangsalder eller som led i behandling af kræft i blærehalskirtel eller bryst)

Nej ☐ *Gå til spørgsmål 24*

Ja ☐ *Besvar nedenstående spørgsmål*

23 Hvornår fik du første gang behandling med kønshormon?

Skriv årstal ca: ☐☐☐☐

24 Har du nogensinde fået tabletter med binyrebarkhormon?

(fx prednisolon, prednison, hydrocortison, medrol)

Nej ☐ *Gå til spørgsmål 26*

Ja ☐ *Besvar nedenstående spørgsmål*

25 Hvornår fik du første gang tabletter med binyrebarkhormon?

Skriv årstal ca: ☐☐☐☐

26 Har du, eller har du haft nogen af disse sygdomme? *(Sæt ét X i hver linje)*

a	Sukkersyge	Nej ☐	Ja ☐	Ved ikke ☐
b	Stofskiftesygdom	Nej ☐	Ja ☐	Ved ikke ☐
c	Ledegigt	Nej ☐	Ja ☐	Ved ikke ☐
d	Knogleskørhed	Nej ☐	Ja ☐	Ved ikke ☐

BAGGRUND OG LEVEVANER

27 Hvor høj er du?

ca: ☐ cm

28 Hvad vejer du?

ca: ☐ kg

29 Hvad vejede du, da du var ca. 25 år gammel?

ca: ☐ kg

30 Har du nogensinde været daglig ryger?

Nej ☐ *Gå til spørgsmål 34*
Ja ☐ *Besvar nedenstående spørgsmål*

31 Hvor mange år har du røget i alt?

(Perioder med rygestop skal trækkes fra) ca: ☐ år

32 Hvor meget har du røget i gennemsnit i de år, du har røget?

ca: ☐ cigaretter per dag
ca: ☐ cerutter eller cigarer per dag
ca: ☐ gram tobak per uge (en pakke indeholder typisk 50 gram)

33 Ryger du for tiden?

Nej ☐ Ja ☐

Spørgsmål 34 – 36 handler om dine sports- og motionsvaner,
da du var ca. 25 år gammel.

34 Dyrkede du sport eller motion mere end 2 timer om ugen?

Nej ☐ *Gå til spørgsmål 37*

Ja ☐ *Besvar nedenstående spørgsmål*

35 Hvor mange timer om ugen dyrkede du sport eller motion?

2-4 timer ☐ 4-6 timer ☐ mere end 6 timer ☐

36 Hvilken type sport eller motion dyrkede du? *(Sæt gerne flere krydser)*

Løb (motion eller konkurrence)	☐
Håndbold	☐
Fodbold	☐
Svømning	☐
Tennis / Badminton / Squash	☐
Volleyball / Basketball	☐
Cykling	☐
Boksning / Brydning	☐
Vægtløftning / Træning i fitnesscenter	☐
Andet	☐

37 Er der nogle af dine forældre eller søskende, som har fået kunstigt knæ eller hofte, før de fyldte 60 år?

Nej ☐ Ja ☐ Ved ikke ☐

38 Må vi kontakte dig per telefon, hvis vi gerne vil have uddybet nogle af dine svar?

☐ Nej tak

☐ Ja, på tlf. nr. ________ eller ________

C. Industry exposure matrix

Industry	*Exposure level*
Agriculture	2
Market gardening	2
Machine pools and landscape gardening	2
Forestry	2
Fishing	2
Extraction of oil and natural gas	1
Extraction of gravel and clay etc	2
Production etc of meat and meat products	2
Manufacturing of dairy products	1
Baker's shops	1
Manufacturing of other food products	2
manufacturing of beverages	1
Manufacturing of tobacco products	1
Manufacturing of textiles	1
Manufacturing of wearing apparel	0
Manufacturing of leather and footwear	0
Manufacturing of wood and wood products	2
Manufacturing of pulp, paper and paper products	2
Publishing of newspapers	1
Publishing activities, excluding newspapers	1
Printing activities	1
Manufacturing of refined petroleum products etc	1
Manufacturing of chemical raw products	1
Manufacturing of paints and soap	1
Manufacturing of pharmaceuticals	1
Manufacturing of rubber and plastic products	1
Manufacturing of glass and ceramic goods	1
Manufacturing of tiles, bricks, cement and concrete	2
Manufacturing of basic metals	2
Manufacturing of building materials of metal	2
Manufacturing of various metal products	1
Manufacturing of marine engines and compressors	1
Manufacturing of ovens and cols-storage plants	1
Manufacturing of agricultural machinery	1
Manufacturing of machinery for industry	1
Manufacturing of domestic appliances	1
Manufacturing of computers and electric motors	0
Manufacturing of radio and communication equipment	0
Manufacturing of medical and optical instruments	0
Building of ships and boats	2
Manufacturing of transport equipment, excl ships	2
Manufacturing of furniture	2
Manufacturing of toys and jewellery	1
Production and distribution of electricity	1
Manufacture and distribution of gas	1
Steam and hot water supply	1

Collection and distribution of water	1
General contractors	2
Bricklaying	2
Installation of electrical wiring and fittings	2
Plumbing	2
Joinery installation	2
Painting and glazing	2
Other construction works	2
Sale of motor vehicles and motorcycles	0
Maintenance and repair of motor vehicles	1
Retail sale of automotive fuel	0
Wholesale (ws) of grain and animal feeds	2
Ws of food, beverages and tobacco	2
Ws of textiles and household goods	1
Ws of wood and construction materials	2
Ws of other raw materials and semi manufactures	1
Ws of machinery, equipment and supplies	1
Other wholesale trade	1
Retail sale of food in non-specialized stores	1
Retail sale of food in specialized stores	1
Department stores	1
Retail sale of pharmaceutical goods and cosmetic articles	1
Retail sale of clothing and footwear	1
Retail sale of furniture and household appliances	1
Retail sale in other specialized stores	1
Repair of household goods	0
Hotels	1
Restaurants	1
Transport via railways and buses	1
Taxi operation and coach services	1
Freight transport by road and via pipelines	1
Water transport	1
Air transport	1
Supporting transport activities	1
Post and telecommunications	1
Financial institutions	0
Mortgage credit institutions	0
Insurance	0
Activities auxiliary to finance	0
Letting of own property	0
Real estate agents	0
Renting of transport equipment and machinery	0
Computer and related services	0
Research and development	0
Legal activities	0
Accounting, book-keeping and auditing	0
Consulting engineers and architects	0
Advertising	0

Building-cleaning activities	1
Other business activities	0
General public service activities	0
Administration of public sectors	0
Defence, police and administration of justice	1
Primary education	0
Secondary education	0
Higher education	0
Adult and other education	0
Hospital activities	1
Medical, dental and veterinary activities	0
Social institutions for children	0
Social institutions for adults	1
Refuse disposal and similar activities	2
Activities of membership organizations	0
Recreational, cultural and sporting activities	0
Other service activities	1
Activity not stated	1

D. Bland-Altman plots for inter-rater agreement

Standing/walking (hours per day)

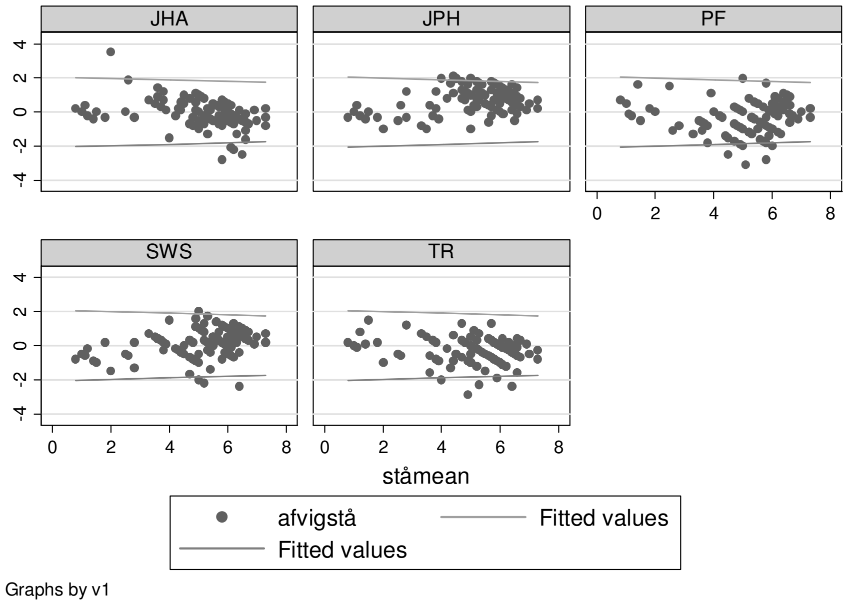


Figure D1.
Bland-Altman plots showing the difference between expert assessment and mean assessment in relation to the mean assessment for standing (afvigstå = difference between expert assessment and mean assessment)
Fitted lines showing the 95% prediction intervals.

Kneeling (hours per day)

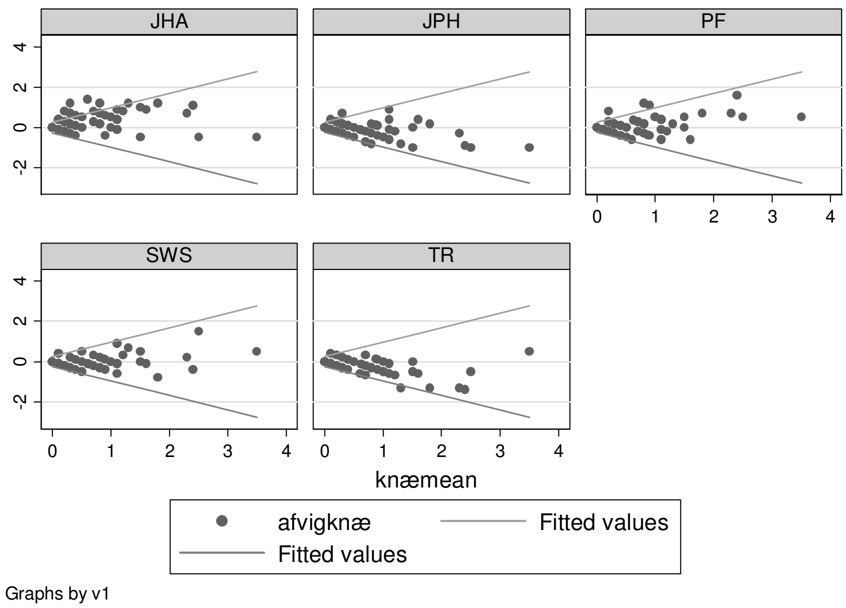


Figure D2.
Bland-Altman plots showing the difference between expert assessment and mean assessment in relation to the mean assessment for kneeling (afvigknæ = difference between expert assessment and mean assessment)
Fitted lines showing the 95% prediction intervals.

Total amount lifted (kg per day)

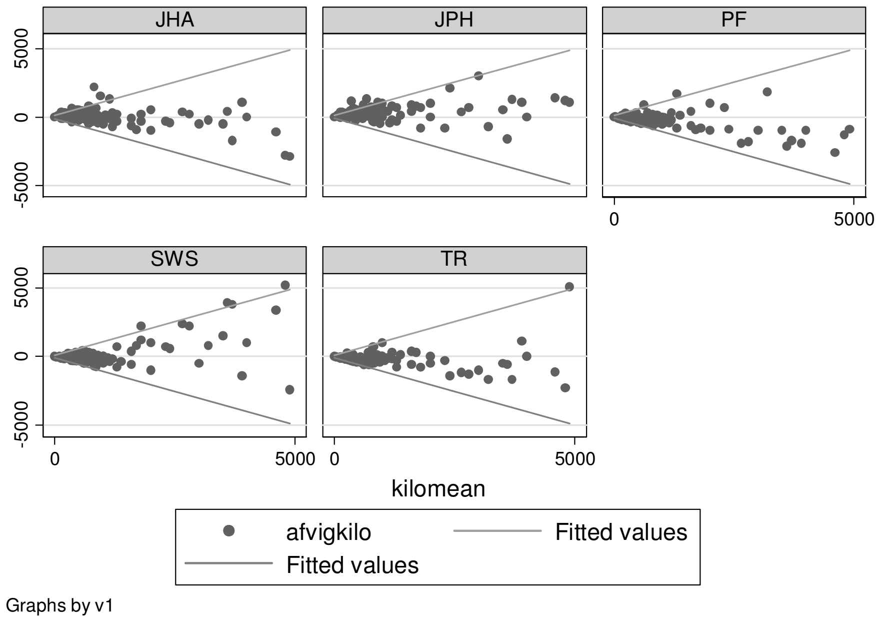


Figure D3.
Bland-Altman plots showing the difference between expert assessment and mean assessment in relation to the mean assessment for total amount lifted (afvigkilo = difference between expert assessment and mean assessment)
Fitted lines showing the 95% prediction intervals.

Lifting more than 20 kg (times per day)

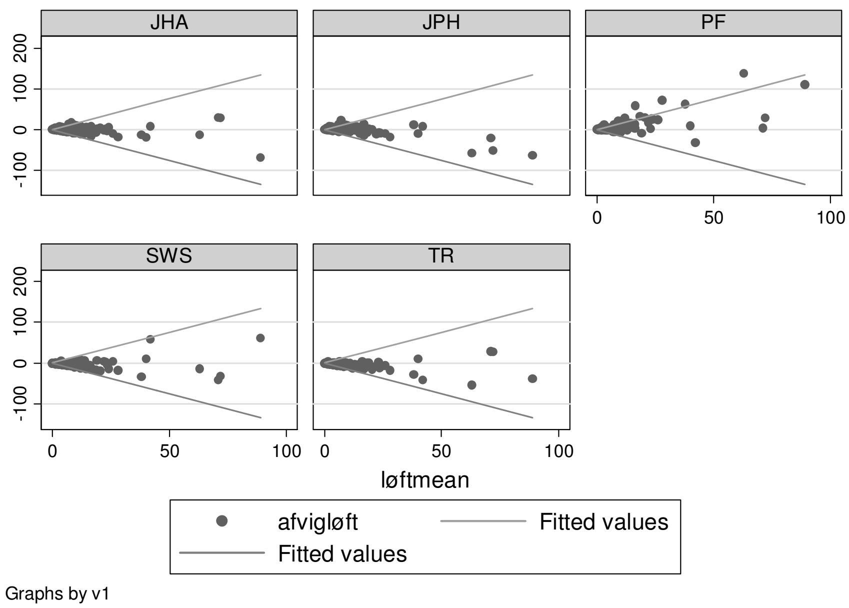


Figure D2.
Bland-Altman plots showing the difference between expert assessment and mean assessment in relation to the mean assessment for lifting more than 20 kg (afvigløft = difference between expert assessment and mean assessment)
Fitted lines showing the 95% prediction intervals.

Whole-body vibration (hours per day)

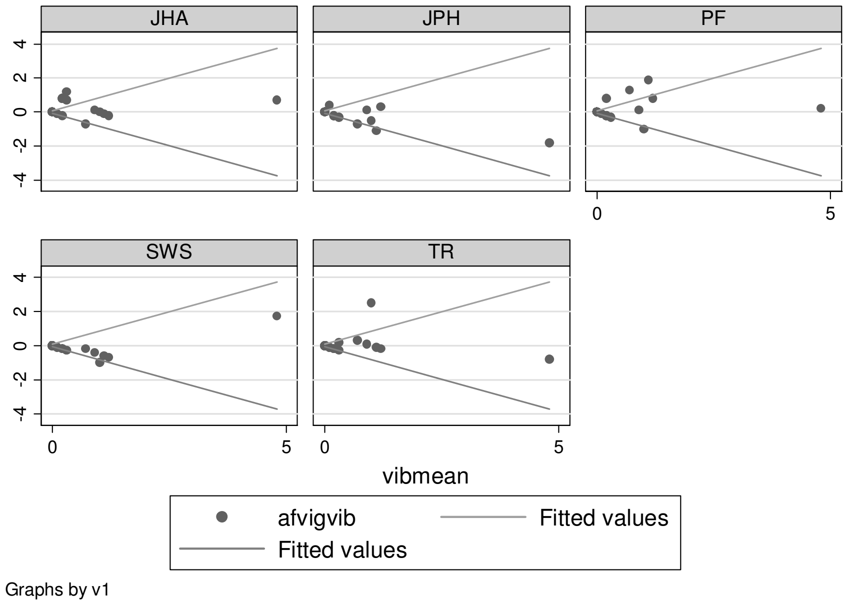


Figure D2.
Bland-Altman plots showing the difference between expert assessment and mean assessment in relation to the mean assessment for whole-body vibration (afvigvib = difference between expert assessment and mean assessment)
Fitted lines showing the 95% prediction intervals.

E. Job exposure matrix

Standing: standing/walking (hours per day), Sitting: sitting (hours per day), Kneeling: kneeling/squatting (hours per day), Vibration: whole-body vibration (hours per day), Kilo: (kg lifter per day, Lifts: number of lifts of 20 kg or above per day

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
1	General managers in agriculture	1231	company secretary, property	4,8	3,0	0,2	1,1	900,0	9,6
	(excluding horticulture	1311	general manager, agriculture (except green houses)						
	and forestry),	No ISCO	farm bailiff						
	dairy, livestock, poultry,	No ISCO	assistant, farm bailiff						
	crop- and animal,and workers	6111	farmworker, skilled/potato						
	not elsewhere classified,	6112	farmer, fruit						
	farm-hands and labourers	6121	farmer, horsebreeding						
	(excluding fruit and	6121	farmer, cattle						
	berry pickers,	6121	farmer, studbreeding						
	and hands in horticulture)	6121	farmer, pig						
		6121	farmer, horse raising						
		6121	farmer, livestock						
		6121	farmworker, skilled/livestock						
		6122	breeder, poultry						
		6122	farmer, poultry/hatching and breeding						
		6122	farmer, egg production						
		No ISCO	farmer, fur/non-domesticated animals (mink)						
		6129	farmer, fur/non-domesticated animals						
		6130	farmer, mixed farming						
		6130	farm worker, skilled/mixed farming						
		9211	groom, stud						
		6122	hatchery worker, skilled/poultry						
		6122	farm worker, skilled/pig						
		9211	hand, farm/livestock						
		9211	labourer, farm						
		9211	stable lad						
		No ISCO	groom						
1	Daily management in	1311	general manager, agriculture (green house)	2,5	5,1	0,3	0,0	620,0	12,0
	market gardening	1311	general manager, agriculture (nursery)						
1	Technicians within agriculture,	3212	technician, forestry	4,4	3,3	0,3	0,1	390,0	2,6
	gardering and forestry	3212	technician, floriculture						
		3212	technician, crop research						
		3212	technician, soil science						
		3212	technician, agronomy						

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
1	People working in forstry	6141	lumberjack	5,9	1,8	0,3	0,9	2650,0	42,0
		9212	labourer, forestry						
		6141	logger						
1	Gardeners in different industries	6113	gardener	6,1	1,1	0,8	0,3	760,0	5,0
		6113	gardener, park						
		6113	greenkeeper						
		6112	landscape gardener						
		6113	nurseryman						
		9211	skilled worker, nursery						
		9211	picker, fruit						
		6113	grower nursery						
		No ISCO	picker, berries						
		6113	gardener, jobbing						
		9211	hand, farm/orchard						
		9141	sexton						
		9312	labourer, digging/grave						
1	Workers in fish farming, including managers	6151	farmer, fish	4,9	2,6	0,3	0,0	720,0	4,6
		6151	hatcher, fish						
		6151	farm worker, skilled/fish						
1	Fishermen and assistants	6152	fisherman, coastal waters	5,2	2,6	0,2	0,0	2000,0	19,0
		6152	fisherman, inland waters						
		No ISCO	fisher, pound net						
		9213	labourer, fiskery						
1	Wokers in quarries	8151	machine-operator, crushing/chemical and related	3,3	4,1	0,3	1,2	820,0	8,0
		8151	machine-operator, mill/chemical and related processes						
		9311	labourer, digging/quarry (gravel)						
		9311	labourer, digging/quarry (stone)						

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
2	Technicians in different manufacturing industries	3113	technician, engineering/electrical systems	3,6	4,1	0,3	0,0	230,0	2,6
		3115	technician, engineering/mechanical/tools						
		3115	technician, engineering/mechanical/machinery						
		No ISCO	technician, engineering/mechanical (offshore)						
		3117	technician, engineering/mechanical (petrol/natural gas)						
		No ISCO	technician, engineering/production (wood)						
		No ISCO	technician, engineering/production (workshop)						
		No ISCO	technician, engineering/roads and transportation						
		3119	technician, engineering/systems (except computers)						
		3145	technician, air traffic safety						
		3145	engineer, flight						
2	People working in the printing industry	3118	draughtsperson, litographic	6,0	1,9	0,1	0,0	810,0	6,2
		3119	technician, engineering/industrial layout						
		7341	photo-type setter, printing						
		7341	layer-on, printing press						
		7341	setter-operator, casting machine/printing type						
		7341	typestter, linotype						
		7341	printer						
		7341	typesetter, phototype						
		7341	imposer, printing						
		7343	developer, photographic plate						
		7343	retocher, printing plates						
		7343	transferrer, litographic						
		7345	bookbinder						
		7346	stenciller, silk-screen						
		7346	printer, silk-screen						
		7346	printer, textile						
		8251	press-operator, printing/offset lithographic						
		8251	press-operator, printing/rotary						
		8251	machine-operator, casting/printing type						
		8251	machine-operator, printing						
		8252	machine-operator, bookbinding						
		8264	machine-operator, dying/garments						
		8264	press-operator, textile						

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
2	People working in the storage industry, excluding managers	4131	clerc, stock	5,5	2,3	0,2	0,2	3600,0	23,4
		4131	storekeeper						
		4131	clerc, freight						
		9333	porter, coldstorage						
		No ISCO	hand, storage						
		No ISCO	hand, coldstorage						
		9333	freight handler						
		No ISCO	hand, lumberyard						
		9333	porter, warehouse						
2	Workers in the rubber industry	8231	machine-operator, vulcanising/rubber goods	6,7	1,1	0,2	0,0	1150,0	6,4
		8231	machine-operator, rubber						
2	Stone cutters and carvers	7113	cutter, stone	6,1	1,6	0,3	0,0	540,0	6,0
		7113	carver, stone						
2	Wood workers, machinery	7423	setter, woodworking machine	6,7	1,0	0,3	0,0	1800,0	22,0
		7423	turner, wood						
		8141	sawyer, sawmill						
		8141	machine-operation, wood processing						
		8141	operator, sawmill						
		8141	press-operator, veneer						
		8240	machine-opeartor, carvin wood						
		No ISCO	hand, saw mill						
		8240	machine-operator, wood products						
		8285	assembler, wood products/venner						
2	Wokers in porcelain and glass industries	8131	machine-operator, glass-production	5,9	2,0	0,1	0,0	670,0	3,4
		8131	machine-operator, ceramics production						
		8131	machine-operator, pottery and porcelain production						
		8131	furnace-operator, glass production						
		8139	machine-operator, mixing glass						
2	Painter, structural steel	7141	painter, structural steel	5,1	2,7	0,2	0,0	210,0	1,2
2	Machine operators withing coating and plating metals	8223	machine-operator, coating metal	6,6	1,4	0,0	0,0	870,0	9,4
		8223	machine-operator, electroplating metal						
		8223	machine-operator, plating metal						
2	Locksmith and related	No ISCO	fitter, lock	5,7	1,9	0,4	0,0	140,0	0,4
		7222	locksmith						

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
2	Machine operators within metal working	7222	toolmaker	6,6	1,3	0,1	0,0	810,0	6,0
		7223	spinner, metal						
		No ISCO	apprentice, machine woker						
		7223	setter-operator, drilling machine/metalworking						
		7223	setter-operator, /metal working						
		No ISCO	polisher						
		7224	polisher, metal						
		8211	press-operator, punching/metal						
2	Maintenance and installation of indutry machinery	No ISCO	smith, machinery	5,9	1,1	1,0	0,0	800,0	11,0
		7233	mechaninc industrial machinery						
		7233	erector-installer, industiral machinery						
2	Machine-operators in the plastic industry	8232	machine-operator, plastic products	6,6	1,3	0,1	0,0	540,0	3,0
		8232	machine-operator, plastics production						
2	Installer and fitters electrical systems and smaller electrical appliances	7241	repairer, electrical equipment	4,9	2,6	0,5	0,0	280,0	1,8
		7241	fitter, electronics/telecommunications equipment						
		No ISCO	installer, alarm systems						
		7241	fitter, electrical/signalling equipment						
		7243	repairer, electronics equipment/television						
		7243	mechanic, electronics						
2	Repairer and installer of tv and radio aerials	7243	erector, television aerial	5,2	2,1	0,7	0,0	230,0	1,2
		7243	repairer, electronics equipment						
2	Mechanincs and technicians, vending machines	No ISCO	technician, engineering/mechanical (vending machines)	5,0	2,6	0,4	0,0	340,0	3,8
		No ISCO	installer, vending machines						
		No ISCO	mechaninc, vending machines						
2	Workers in slaughter houses	7411	maker, string/gut	7,3	0,7	0,0	0,0	3500,0	26,0
		7411	slaughterer						
		7411	smokehouse worker, meat						
		7411	boner, meat						
		7411	maker, sausage						
		7411	dresser poultry						
		7411	cutter, meat						

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
2	Workers in bakeries, excluding attendants in bakery shops	1312	general manger, bakery	7,3	0,7	0,0	0,0	380,0	6,0
		7412	maker, pastry						
		7412	baker						
		7412	tablehand, baker						
		8274	machine-operator, bakery products						
2	Workers in dairywork	7413	maker, dairy products	6,6	1,3	0,1	0,0	1200,0	9,0
		7413	maker, cheese						
		8272	machine-operator, dairy products						
2	Cutter, garments and textiles	7435	cutter, garment	6,0	2,0	0,0	0,0	260,0	1,4
2	Upholstrers	7437	upholster, automobile	5,8	2,0	0,2	0,0	380,0	4,2
		7437	upholstrer, vehicle						
		7437	upholstrer, furniture						
2	Leather workers	7441	dyer-stainer, leather	6,5	1,5	0,0	0,0	702,0	3,4
		7441	classer, skin						
		8265	machine-operator, washing/hide						
		8265	machine-operator, hide processing						
2	Workers in shipyards	No ISCO	shipyeard worker	6,2	1,0	0,8	0,0	700,0	8,4
2	Workers in iron and steel production	8121	furnace-operator, converting/steel	7,0	1,0	0,1	0,0	660,0	7,4
		8122	furnace-operator, melting/metal						
		8122	operator, rolling-mill/steel						
		8122	machine-operator, casting/metal						
		8123	machine-operator, mixing/metal						
2	Workers in brickyards	No ISCO	labourer, brickyard	6,1	1,8	0,1	0,2	1300,0	28,0
		8131	kiln-operator, brick and tile						
2	Workers in packing departments of different kinds	9322	packer, hand	6,2	1,8	0,0	0,2	2800,0	24,0
		No ISCO	hand, packing department						
2	Industrial painters and car painters	7142	painter, vehicle	6,6	0,8	0,6	0,0	335,0	2,6
		7142	painter, automobile						
		7142	sprayer, metal						
		8223	machine-operator, painting/metal						
		8223	machine-operator, spraying/metal						

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
2	Workers in paper and cardboard production	8143	machine-operator, papermaking	6,5	1,5	0,0	0,2	1600,0	18,4
		8253	machine-operator, paper products						
		8253	machine-operator, paper box production						
		8253	machine-operator, cardboard products						
		8290	machine-operator, labelling						
2	Machineoperators in textile industry	8261	machine-operator, spinning/thread and yarn	6,4	1,5	0,1	0,0	670,0	3,2
		8261	machine-operator, spinning/synthetic fibre						
		8261	machine-operator, winding,thread and yarn						
		8262	machine-operator, weaving/jacquard						
		8262	machine-operator, knitting						
		8262	operator, loom/jacquard						
		8262	machine-operator, weaving						
		8262	machine-operator, knitting/garment						
2	Sewers of clothing and other textiles	8263	sewer	1,2	6,8	0,0	0,0	210,0	0,6
		8263	sewer, garments						
		8263	machine-operator, sewing						
		7436	sewer, textile						
2	Machine-operators, dying of textile and fabrics	8264	machine-operator, dying/fabric	5,3	2,7	0,0	0,0	350,0	4,2
		8264	machine-operator, dying/textile fibres						
2	Workers in the fish-processing industry	7411	cutter, fish	7,3	0,7	0,0	0,0	1200,0	10,0
		8271	machine-operator, fish products						
		No ISCO	sorter, fish						
2	Workers in the food producing insudtry (sweets, coffee, tobacco and sugar)	8274	machine-operator, confectionary production	5,7	2,3	0,0	0,0	620,0	1,4
		8274	machine-operator, chocolate products						
		No ISCO	machine-operator, buscuit-products						
		8276	machine-operator, sugar production						
		8276	machine-operator, refining/sugar						
		8277	machine-operator, roasting equipment/coffee						
		8279	machine-operator, toacco products						
2	Workers in breweries	8278	kiln-operator, malting/spirits	5,0	3,0	0,0	0,0	490,0	3,2
		8278	brewer						
2	Machine-operator, winding/transpormer coil	8282	machine-operator, winding/transpormer coil	2,0	6,2	0,0	0,0	240,0	1,4

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
2	Assemblers of small electrical appliances	8283	assembler, electronic components	1,1	6,9	0,0	0,0	220,0	0,4
		8283	assembler, radio						
		8283	assembler, electronic equipment						
2	Labourer in production industries	No ISCO	hand, production	5,0	3,0	0,0	0,3	1000,0	15,0
3	Technicians within gas, electrical power, heating, etc.	3113	technician, enginieering/electrical	4,5	3,0	0,5	0,0	330,0	2,6
		3113	technician, enginieering/electrical (electric power dist)						
		3115	technician, engineering/mechanical (refrigeration)						
		No ISCO	teechnician, engineering/mechanical (gas)						
		3115	technician, engineering/mechanical (heating/ventilation etc)						
		3119	technician, engineering/production						
3	Operators at boiler plants or power plants	8161	operator, generator/electricpower	4,0	3,8	0,2	0,0	380,0	2,4
		8162	operator, bolier plant/steam						
4	Daily management in construction businesses	1223	department manager, production and operations	2,6	5,3	0,1	0,0	130,0	1,0
		No ISCO	contractor, labour						
		1313	general manager, construction						
4	People working with surveying	2148	cartographer	3,5	4,5	0,0	0,0	64,0	0,0
		3112	estimator, engineering/civil						
		3112	technician, engineering/civil (soil mechanincs)						
		2148	surveyor						
4	Thatchers	7131	thatcher	4,7	0,9	2,4	0,0	1000,0	9,0
4	Paviours	7122	paviour	4,7	0,8	2,5	0,0	3700,0	16,6
		No ISCO	hand, paviour						
4	Bricklayers and stonemasons	7122	stonemason, construction	5,8	0,7	1,5	0,0	2400,0	12,0
		7132	layer, tile						
		7122	bricklayer, construction						
4	Terazzo and marble workers	7113	polisher, marble	6,4	0,7	0,9	0,0	900,0	7,2
		7123	terazzo worker						

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
4	Wood working, craftmanship	7124	joiner	5,8	0,6	1,5	0,0	1600,0	11,0
		No ISCO	apprentice, joiner						
		7124	joiner, construction						
		7124	boatbuilder, wood						
		7124	carpenter						
		No ISCO	erector, green house						
		7129	housebuilder, non trditional materials						
		7214	shipwright, metal						
		7422	maker, model/wooden						
		7422	cabinetmaker						
		No ISCO	builder, model						
		8285	assembler, furniture/wood and related materials						
		No ISCO	finisher, furniture						
		No ISCO	hand, carpenter						
4	Workers in drainage and sewage	7129	layer, drain	5,2	1,5	1,3	0,7	1200,0	11,4
		No ISCO	worker, sewer						
		No ISCO	sewer contractor						
4	Workers within scaffolding	7129	scaffolder	6,6	0,7	0,7	0,0	4800,0	89,0
		7129	rigger, scaffolding						
4	Roofers of different kinds	7131	roofer	5,7	0,7	1,6	0,0	1300,0	16,0
		8151	roofer, composit material						
4	Floor layers of differnt kinds	7132	parquetry worker	3,8	0,7	3,5	0,0	700,0	10,4
		7132	floor layer, parquetry						
		No ISCO	floor-layer, carpet						
4	Insulations workers	7134	insulation worker	5,2	1,0	1,8	0,0	400,0	3,6
		No ISCO	hand, insulation worker						
4	Plumbers and pipe fitters/layers	No ISCO	fitter, pipe/gas	4,8	1,1	2,3	0,0	590,0	7,4
		7136	plumber						
		7136	fitter, pipe						
		7136	layer, pipe						
		7213	boilersmith						
4	Glazier	7135	glazier	6,2	1,3	0,5	0,0	800,0	13,6

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
4	Electricians and fitters	7136	fitter, pipe/ventilation	5,5	1,4	1,1	0,0	260,0	3,2
	of ventilation	7137	electrician, building/electrical installation						
		7137	electrician, building repairs						
		7137	electrician						
4	Painters and wallpaper hangers	7141	painter-decorator, wallpapering	6,1	0,8	1,1	0,0	380,0	4,4
		7141	painter, ship's hull						
		No ISCO	apprentice, painter						
		7141	painter, building						
		7141	wallpaper hanger						
		7141	painter, house						
		7141	painter-decorator, wallpapering						
		9313	handyman, building maintenance						
4	Moulders in the metal industry	7211	moulder, metal castings/bench	6,3	1,6	0,1	0,0	1000,0	8,0
		No ISCO	moulder						
		7211	moulder, metal castings/pit						
		7211	moulder, metal castings						
		8211	machine-operator, moulding/metal						
4	Welders	No ISCO	assistant, welder	6,0	0,9	1,1	0,0	510,0	9,0
		7212	welder						
4	Concrete and cement workers	8123	furnace-operator, hardening	6,6	1,3	0,1	0,0	2300,0	23,0
		7123	caster, concrete products						
		8212	machine-operator, asbestos-cement products						
		8212	machine-operator, cement products						
		8212	machine-operator, comcrete-mixing plant						
		7123	mixer, concrete						
		8212	machine-operator, cast-concrete products						
4	Smiths of different kinds	7221	smith, anvil	6,0	1,0	1,0	0,0	700,0	12,0
		7221	hammer-smith						
		7221	toolsmith						
		No ISCO	apprentice, smith(building)						
		7221	blacksmith						
		No ISCO	appentice, smith						
		No ISCO	smith (building)						
		No ISCO	metal worker						
		8211	machine-operator, shaping/metal						

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
4	Mechanincs and installers cranes, elevators and ships	No ISCO	mechanic/erector, crane	5,8	1,3	0,9	0,2	700,0	9,0
		7233	fitter, enginn/marine						
		7241	fitter, electrical/elevator and related equipment						
4	Operators of drilling and digging equipment	8113	operator, drilling equipment/rotary	5,0	1,6	0,6	0,0	1000,0	9,8
		8113	operator, drilling equipment/cable (oil and gas well)						
		8113	operator, boring equipment/wells						
		8332	operator, digger/trench digging						
		8332	driver, trench-digging machine						
		8332	driver, excavating machine						
		9312	labourer, digging/trench						
4	Drivers of entrepeneur machinery and tractors	8331	driver, tractor	1,5	6,5	0,0	4,8	280,0	3,8
		8332	operator, road-roller						
		8332	driver, bullldozer						
		8333	operator, chair-lift						
		8333	operator, crane						
4	Workers in road and building construction	9312	land clearer	5,6	1,3	1,1	1,0	3000,0	20,4
		9312	labourer, maintenace/roads						
		No ISCO	hand, contractor (labour)						
		9312	labourer, construction						
		No ISCO	hand, building site						
		9313	labourer, construction/buildings						
4	Construction worker, concerned with binding of iron	No ISCO	iron binder, construction	6,3	0,6	1,1	0,0	1700,0	10,0
4	Bricklayer's assistan	No ISCO	bricklayer's assistant	6,9	0,4	0,7	0,0	4600,0	40,0
4	Labourer in construction with raising buildings	No ISCO	worker, construction	6,1	1,0	0,9	0,0	1375,0	16,3
5	Merchants of animals for farming	1314	merchant, wholesale trade - pigs	3,6	4,0	0,2	0,0	160,0	2,0
		1314	merchant, wholesale trade - cattle						
		1314	merchant, wholesale trade - horses						
5	People working with handling and buying/selling of scrap and used metal	1314	merchant, wholesale trade - iron and metal	3,7	3,9	0,4	0,0	950,0	14,2
		No ISCO	car breaker						

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
5	Merchants/owners	1224	general manager, retail trade	5,9	2,1	0,1	0,0	1100,0	12,0
	of smaller businesses	1314	merchant, retail trade (small animals)						
		1314	merchant, retail trade (bicycles)						
		1314	merchant, retail trade (cheese)						
		1314	merchant, retail trade (magasines)						
		1314	merchant, retail trade (small electrical appliances)						
		1314	merchant, retail trade (fish)						
		1314	merchant, retail trade (vine)						
		1314	merchant, retail trade (fruits)						
		1314	general manager, retail trade (paints and wall-paper)						
		1314	merchant, retail trade (carpets)						
		1314	general manager, wholesale trade (flowers)						
		1314	merchant, retail trade (ladies clothing)						
		1314	merchant, retail trade (clothing)						
		1314	merchant, retail trade (groceries)						
		1314	merchant, retail trade (lumber)						
		1314	general manager, retail trade (hardware store)						
		1314	general manager, retail trade (news paper stand)						
		1314	merchant, retail trade (flowers)						
		1314	merchant, retail trade (vegetables)						
		1314	general manager, retail trade (co-op)						
5	Attendants and managers of	1314	general manager, retail trade (service station)	5,7	2,3	0,0	0,0	400,0	4,0
	service stations	5220	attendant, petrol pump						
		5220	attendant, service station/automobiles						
5	Owner and managers in	1225	department manager, production and operations/restaur	5,0	2,9	0,1	0,0	460,0	6,0
	the restaurant business	1315	general manager, inn						
		1315	innkeeper						
		1315	general manager, canteen						
		1315	general manager, cafe						
		1315	barkeeper						

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
5	People owing, managing or working with maintenance of sports areas, buildings, camping- and campsites	1315	general manager, camping site	5,4	2,4	0,2	0,0	450,0	5,2
		No ISCO	general manager, camp						
		1319	general manager, sporting activities						
		3151	inspector, building						
		9141	caretaker, building/cleaning						
		9141	caretaker, building						
		9141	caretaker, building (school)						
		9141	janitor						
5	Managers of storage facilities and distribution of goods	1316	general manager, storage	3,8	4,1	0,0	0,0	590,0	4,4
		No ISCO	general manager, depot (beer)						
		No ISCO	general manager, message office						
		1317	general manager, business services						
		No ISCO	distributor, tableware						
5	People working with food preparation in different types of kitchens	3223	nutritionist	6,6	1,3	0,1	0,0	440,0	3,2
		No ISCO	catering officer						
		5121	butler						
		No ISCO	manager, cafeteria						
		No ISCO	manager, take-out						
		5122	cook, ship's mess						
		No ISCO	assistant, cook						
		No ISCO	manager, kanteen						
		5122	cook						
		No ISCO	manager, kitchen						
		No ISCO	manager, café						
		No ISCO	sandwich maker						
		9132	helper, kitchen/non-domestic						
		No ISCO	hand, cafeteria						
		9132	hand, kitchen						
		9132	washer, hand/dishes						
5	People travelling within sales	3415	representative, sales commercial	2,8	5,2	0,0	0,0	195,0	1,4
		3415	agent, sales/commercial						
		3415	commercial taveller						
		3415	salesperson, commercial						
		3415	salesprson, travelling						
		3417	appraiser						

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
5	Waiters and bartenders	5123	bartender	6,6	1,3	0,1	0,0	560,0	3,4
		5123	waiter						
		5123	waitress						
		5123	waiter, head						
5	Attendants in different shops, excluding service stations	No ISCO	clerk, postal services	6,1	1,9	0,0	0,0	620,0	3,0
		5220	attendant, shop						
		5220	attendant, shop (shoe)						
		5220	attendant, shop (photo)						
		5220	attendant, shop (pharmacy)						
		5220	attendant, shop (flowers)						
		5220	attendant, shop (groceries)						
		5220	attendant, shop (delicacy)						
		5220	attendant, shop (books)						
		5220	attendant, shop (lumberjard)						
		5220	attendant, shop (hardware store)						
		5220	attendant, shop (news paper stand)						
		5220	attendant, shop (co-op)						
		5220	attendant, shop (clothing)						
		5220	attendant, shop (paints)						
		5220	attendant, shop (sports equipment)						
		5220	attendant, shop (sales)						
		5220	attendant, shop (bakery)						
5	Cleaner of vehicles	9142	cleaner, vehicle	6,2	1,3	0,5	0,0	190,0	0,4
		9142	washer, hand/vehicle						
5	Sheet metal workers, working with metal for vehicles	No ISCO	coach-builder	6,1	0,7	1,2	0,0	560,0	7,2
		7213	maker, metal sheet						
		7213	sheet-metal worker, vehicles						
		7213	beater, vehicle panel						
		7213	sheet metal worker, vehicles						
		8211	machine-operator, planing metal						

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
5	Mechanics of vehicles,	7135	glazier, vehicle	6,1	1,0	0,8	0,0	540,0	9,0
	planes and motorcycles	No ISCO	repairer, vehicles						
		7231	mechanic, enginve/motor vehicle						
		7231	mechanic, motor cycle						
		7231	mechanic, motor vehicle						
		7231	mechanic, automobile						
		7233	mechanic, engine/aircraft						
		7241	electrician, vehicle						
		7241	electrician, aircraft						
		No ISCO	assembler, tire						
5	Bicycle and moped repairer	No ISCO	repairer, moped	6,2	1,0	0,8	0,0	320,0	4,8
		7231	repairer, bicycle						
6	People working in the	3141	chief engineer, ship	4,7	3,0	0,3	0,1	460,0	6,0
	machineroom in ships	3141	superintendent, marine/technical						
		8340	boatman						
6	Post delivering and sorting	4142	postman	6,4	1,5	0,1	0,0	390,0	6,4
		4142	mailman						
6	Attendants in travelling sevices,	5111	attendant, fligt	6,0	1,8	0,0	0,0	340,0	0,4
	excluding trains	5111	puser, aircraft						
6	Attendants and drivers, trains	5112	conductor, train	4,5	3,5	0,0	0,0	130,0	0,6
		No ISCO	attendant, train						
		8311	driver, train						
		8311	driver assistant, train						
		8311	driver, locomotive						
6	Working with lines and kables	7245	wire worker, telephone	5,2	1,8	1,0	0,0	450,0	3,4
	for telephone	7245	cable worker, telegraph						
	and electric power	7245	line worker, telephone						
		7245	line worker, electric power						
		7245	cable worker, electric power/overhead cables						
6	Drivers of busses	8323	driver, bus	0,8	7,2	0,0	0,0	360,0	7,8
		8323	driver, motorbus						
		8323	driver, trolley-bus						
		8323	driver, moterbus						

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
6	Railway workers, excluding drivers of trains	8312	coupler, railway yard	4,9	2,9	0,2	0,0	320,0	6,8
		8312	guard, goods train						
		8312	signaller, railway						
		8312	shunter, railway						
		No ISCO	worker, engine shed						
		9312	trackman, railway						
6	Drivers of cars, including driving instructors	3340	instructor, driving	1,0	7,0	0,0	0,0	100,0	1,6
		8322	driver, taxi						
		8322	chauffeur, motor-car						
		8322	driver, motor-car						
6	Drivers of lorries of diferent kinds,excluding draymen	No ISCO	driver, fire-engine	1,4	6,6	0,0	0,0	1800,0	14,4
		8324	driver, lorry						
		8324	driver, tanker						
		8324	driver, trailer-truck						
		8324	driver, truck						
		No ISCO	driver, postal services						
		9333	loader, road vehicles/lorry						
		9333	handler, freight						
		9333	porter, goods-loading						
6	Drayman	No ISCO	drayman	3,9	4,1	0,0	0,0	3200,0	63,0
6	Driver of fork-lift truck	8334	operator, truck/fork-lift	1,8	6,2	0,0	0,0	560,0	5,4
6	Workers in ships, excluding those working in the engine room and those working with fishery	8340	crewman	5,6	2,3	0,1	0,0	560,0	6,4
		8340	sailor						
		8340	hand, deck						
		8340	seaman, able						
		8340	seaman, ordinary						
		8340	boatswain						
6	Messenger boy, deliverer etc. mainly by foot or bicycle	9151	messenger boy	6,4	1,6	0,0	0,0	295,0	2,0
		9151	post-runner						
		No ISCO	deliverer, bicycle						
		9151	messenger						
		9151	deliverer, hand/newspaper						
		No ISCO	messenger, bank						
		9151	runner, messages						

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
6	Rigger	7215	rigger	6,2	1,0	0,8	0,0	900,0	13,0
6	Workers within loading and unloading goods from ships	9211	labourere, roustabout	6,6	1,4	0,0	0,0	4000,0	38,0
		9333	stevedore						
		9333	loader boat						
		No ISCO	unloader, boat						
		9333	Docker						
6	Furniture movers	9333	remover, furniture	5,3	2,6	0,1	0,0	3900,0	71,0
		9333	furniture mover						
6	Loader in airports	9333	loader, aircraft	5,4	1,9	0,8	0,0	4900,0	72,0
7	Cleaners (all) and porters (hospitals)	No ISCO	hospital porter	6,6	1,4	0,0	0,0	630,0	8,4
		9132	cleaner, hotel						
		No ISCO	hand, hospital						
8	People working in dry-cleaning	1318	general manager, cleaning	6,0	1,9	0,1	0,0	600,0	1,8
		9133	dry-cleaner, hand						
		9133	spotter, dry-cleaning						
8	Veterinarian work	2223	veterinarian	4,2	3,8	0,0	0,0	280,0	1,4
		No ISCO	nurse at veterinarian						
8	People working behind the scenes at theaters and film sets	1229	stage manager	4,4	3,3	0,4	0,0	590,0	6,0
		No ISCO	stage hand						
		No ISCO	stage worker						
8	People working with care-taking, excluding nurses	5132	orderly	5,3	2,4	0,4	0,0	1050,0	10,0
		No ISCO	helper, disabled at home						
		5132	attendant, nursing/except home						
		No ISCO	aid, nursing/hospital (evening shift)						
		5133	aid, nursing/home						
		5132	aid, nursing/hospital						
		5133	attendent, nursing/home						
8	Nurses	2230	nurse, professional/district	5,0	3,0	0,0	0,0	320,0	3,6
		2230	nurse, professional/clinic						
		2230	nurse, professional/charge						
		No ISCO	apprentice, nurse						
		3231	nurse, associate professional						
		No ISCO	nurse, evening shift						

9-group	HEG heading	ISCO	International occupational title	Standing	Sitting	Kneeling	Vibration	Kilo	Lifts
8	Artists	No ISCO	dancer	5,8	1,9	0,3	0,0	350,0	7,0
		3474	acrobat						
8	Docotors	2221	anaesthetist	4,3	3,7	0,0	0,0	80,0	0,4
		2221	physician						
		2221	surgeron, orthopaedic						
		2221	medical practitioner						
		2221	surgeon						
		2221	doctor, medical						
8	Hairdressers and barbers	5141	hairdresser, women	5,5	2,5	0,0	0,0	30,0	0,0
		5141	barber						
		5141	hairdresser, men						
		5141	hairdresser						
		No ISCO	hand, hair dresser						
8	Ambulance workers	No ISCO	paramedic	2,8	5,1	0,2	0,0	650,0	13,0
		5132	ambulance man						
8	Chimney sweep	7143	chimney sweep	4,9	2,3	0,8	0,0	190,0	1,2
8	People working with laundry	9133	laundrer, hand	6,6	1,4	0,0	0,0	800,0	8,0
		9133	washer, hand/laundry						
8	Window cleaners	9142	cleaner, windows	6,0	1,7	0,3	0,0	170,0	3,0
8	Attendants and meter readers, cor parking. Here parking in the streets, not closed lots	No ISCO	attendant, parking/street	6,6	1,4	0,0	0,0	0,0	0,0
		No ISCO	meter reader (parking)						
8	Workers in garbage disposal and collection	9161	colelctor, refuse	5,9	2,1	0,0	0,0	2000,0	16,6
		9161	collector, garbage						
		9162	sweeper, street						

9-group: 1) Agriculture, fishing and quarrying - 2) Manufacturing - 3) Electricity and water supply - 4) Construction
5) Retail- and wholesale trade, hotels and restaurants - 6) Tranport, post and telecommunication
7) Finance andbusiness services - 8) Public and privat services - 9) No activity stated

F. Stata programming code

Preparing for logistic regression

Stata program written by Michael Væth, Professor, Department of Biostatistics, School of Public Health, Aarhus University, Denmark.

Definition of necessary variables
pnr: name of unique identification of subjects
newstart = either first year of follow-up or the year of reaching 10 years of full-time employment during the follow-up period: name of variable for first year of follow-up
opyear= year of receiving THR due to any diagnosis: name of variable defining year of surgery
hipop1: name of variable defining that a subject have received THR due to primary osteoarthritis
Interval: name of variable defining number of years from **newstart** to final year of follow-up
byear: name of variable defining year of birth
cumstart: name of variable defining accumulated exposure at the start of follow-up
pointaar1996: name of variable defining exposure accumulated in 1996 (equals 0 if no exposure is accumulated, either because of job without exposure, or not being employed)
pointaar1997: name of variable defining exposure accumulated in 1997 (and so forth for the next years)

```
Use "dataset.dta", clear

*Expand for each subject, making one line for each number of intervals
expand interval. Hence, there is "interval" identical lines for each
subject
sort pnr

*Numbering each line for each subject
by pnr: gen antal = _n

*Each line per subject needs an individual calendar year
*First line gets the year equal to "newstart"
*Next line gets the year of "newstart" + 1
*The following line gets the year of "newstart" + 2 and so on
*In this case there is a possibility of up to 11 years ("newstart", and the
*following 10 years

by pnr: gen calenderyear = newstart if antal==1
by pnr: replace calenderyear = newstart+1 if antal==2
by pnr: replace calenderyear = newstart+2 if antal==3
by pnr: replace calenderyear = newstart+3 if antal==4
by pnr: replace calenderyear = newstart+4 if antal==5
by pnr: replace calenderyear = newstart+5 if antal==6
by pnr: replace calenderyear = newstart+6 if antal==7
by pnr: replace calenderyear = newstart+7 if antal==8
by pnr: replace calenderyear = newstart+8 if antal==9
by pnr: replace calenderyear = newstart+9 if antal==10
by pnr: replace calenderyear = newstart+10 if antal==11

*Generating a case variable for the year, where the subject actually
*becomes case
*It is only possible to be a case in the last year
*The subject becomes a case if "hipop1" and "opyear" are both present,
*and "opyear" and "calenderyear" are equal

gen case = 1 if calenderyear==opyear & hipop1==1
replace case = 0 if case==.

*tabulating how many cases are present
tab case
```

```
*Age in whole years are calculated for each "calenderyear" for each subject
gen calenderage = calenderyear-byear

*calculating the cumulated exposure for each "calenderyear" for each
subject
*********************************'
by pnr: gen cumexpo = cumstart if antal==1
by pnr: replace cumexpo = cumstart + pointaar1996 if antal==2
by pnr: replace cumexpo = cumstart + pointaar1996 + pointaar1997 if
antal==3
by pnr: replace cumexpo = cumstart + pointaar1996 + pointaar1997 +
pointaar1998 if antal==4
by pnr: replace cumexpo = cumstart + pointaar1996 + pointaar1997 +
pointaar1998 + pointaar1999 if antal==5
by pnr: replace cumexpo = cumstart + pointaar1996 + pointaar1997 +
pointaar1998 + pointaar1999 ///
+ pointaar2000 if antal==6
by pnr: replace cumexpo = cumstart + pointaar1996 + pointaar1997 +
pointaar1998 + pointaar1999 ///
+ pointaar2000 + pointaar2001 if antal==7
by pnr: replace cumexpo = cumstart + pointaar1996 + pointaar1997 +
pointaar1998 + pointaar1999 ///
+ pointaar2000 + pointaar2001 + pointaar2002 if antal==8
by pnr: replace cumexpo = cumstart + pointaar1996 + pointaar1997 +
pointaar1998 + pointaar1999 ///
+ pointaar2000 + pointaar2001 + pointaar2002 + pointaar2003 if antal==9
by pnr: replace cumexpo = cumstart + pointaar1996 + pointaar1997 +
pointaar1998 + pointaar1999 ///
+ pointaar2000 + pointaar2001 + pointaar2002 + pointaar2003 + pointaar2004
if antal==10
by pnr: replace cumexpo = cumstart + pointaar1996 + pointaar1997 +
pointaar1998 + pointaar1999 ///
+ pointaar2000 + pointaar2001 + pointaar2002 + pointaar2003 + pointaar2004
+ pointaar2005 if antal==11

*Looking at "cumexpo" in order to establish cut-off levels for the
different groups
codebook cumexpo

*generating exposure groups "expogr" based on the codebook just made
egen expogr = cut(cumexpo), at (0, 0.001, 10, 20, 30, 40, 90) label
*These leves are just shown for illustrative purposes, and not the actual
*ones from the study
```

Case-control sampling

Stata program written by Morten Frydenberg, associate professor, MSc, PhD, Department of Biostatistics, School of Public Health, Aarhus University, Denmark.

Definition of necessary variables
sex: name of gender defining variable
birthday: name of variable defining date of birth
indday = date of first THR due to primary OA: name of variable defining date of subject becoming a case
year10 = calendar year of reaching 10 years of full-time employment: name of variable defining calendar year after which a subject can become a case

```
use “dataset.dta”, clear

*THR surgeries before January 1, 2005 can not become cases
drop if indday<mdy(1,1,2005)

*THR surgeries before reaching 10 years of full-time employment cannot be
used
*These subjects can not be used as controls either
drop if year(indday)<=year10

*Subjects can not become cases or controls if reaching 10 years of full-
time *employment after December 31, 2006 or if year of reaching 10 years of
full-time *employment is missing
drop if year10>2006

*definition of case
generate case=1 if indday<mdy(1,1,2007)

sort sex birthday indday

*Finding out how many cases have the same gender and birthday
by sex birthday: egen ncases=total(case)

*generating stratae, with independent names
generate long strata=birthdate*10+sex

*Size of the different strataes
by sex birthdate: gen nstrata=_N
by sex birthdate: gen stratano=_n

*distribution of cases and stratae
tabu ncases if stratano==1
sum ncases
local maxcases=r(max)

*generate start dataset with only one person
preserve
drop if _n>1
gen strata2=0
save liste.dta, replace
restore

*now each strata is formed with the case as the first entry
*but sampled in a random order
foreach ZZ of numlist 1/`maxcases’ {
gen dum=-1 if stratano==`ZZ’
sort strata dum
drop dum
*save dataset
preserve
```

```
*drop if index date is before date of reaching 10 years of employment
by strata: drop if year(indday[1]) <=year10
*drop if case and control have identical index date
by strata: drop if indday==indday[1]&_n>1
*save case and two controls
by strata: drop if _n>3
*name strata to be identifiable later
gen strata2=`ZZ'
*append to already exiting dataset
append using liste.dta
save liste, replace

drop if ncases<=`ZZ'
drop if stratano<=`ZZ'
}

*drop first strata with only one person (by definition)
use liste.dta, clear
drop if strata2==0
save liste.dta, replace
```

G. Descriptive tables

Table 1G.
Descriptive information on the distribution of follow-up time, number of cases, age at start of fololw-up, and socioeconomic status at the age 40-55 accoding to cumulative exposure groups for women.

	Cumulative exposure (point-years)*					
	0	>0 – 5	6 – 15	16 – 25	26 +	Total
Follow-up (years)	323,233	2,110,311	3,396,281	2,162,062	1,134,723	9,126,600
Cases	515	1720	3159	2109	1281	8784
Age in years (SD)	51.5 (11.4)	46.4 (9.4)	47.3 (10.0)	50.2 (9.3)	53.0 (8.3)	48.2 (9.9)
Socioeconomic status at age 40-55, number (%)						
Self-employed and their spouses	956 (2.7)	10,549 (4.3)	23,773 (6.3)	5,361 (3.0)	863 (1.4)	41,502 (4.6)
Top leaders in business and organisations and highly skilled white collar workers	1571 (4.3)	7867 (3.2)	8445 (2.2)	4841 (2.7)	2542 (4.2)	25,266 (2.8)
White collar workers and skilled blue collar workers	18,513 (52.0)	114,437 (46.4)	149,997 (39.8)	82,616 (46.0)	31,471 (52.0)	397,034 (44.1)
Unskilled blue collar workers and workers without mention of skill level	12,778 (35.9)	86,238 (35.0)	160,224 (42.5)	80,530 (44.8)	24,703 (40.8)	364,473 (40.5)
Persons outside the labour market	1817 (5.1)	27,446 (11.1)	34,711 (9.2)	6355 (3.5)	945 (1.6)	71,274 (7.9)

* Point-years = years of full-time employment weighted by score of physical work load in employment industry

Table 2G.
Descriptive information on the distribution of follow-up time, number of cases, age at start of follow-up, and socioeconomic status at the age 40-55 according to cumulative exposure groups for men.

	Cumulative exposure (point-years)*						
	0	>0 – 5	6 – 15	16 – 25	26 – 35	36+	Total
Follow-up (years)	186,236	1,146,384	2,617,028	2,748,192	2,090,511	1,509,051	10,297,402
Cases	242	755	2075	2447	2335	2046	9990
Age in years (SD)	55.6 (11.5)	46.0 (9.1)	46.3 (10.5)	48.6 (10.5)	53.5 (9.0)	55.7 (7.6)	49.1 (10.5)
Socioeconomic status at age 40-55, number (%)							
Self-employed and their spouses	1121 (5.2)	11,187 (8.2)	48,239 (15.2)	26,885 (9.8)	7951 (4.6)	2694 (3.1)	98,077 (9.7)
Top leaders in business and organisations and highly skilled white collar workers	4843 (22.6)	16,928 (12.4)	29,149 (9.2)	27,229 (9.9)	22,738 (13.2)	11,697 (13.3)	112,584 (11.1)
White collar workers and skilled blue collar workers	12,052 (56.3)	69,699 (51.2)	107,004 (33.7)	89,793 (32.6)	74,701 (43.5)	39,240 (44.5)	392,489 (38.8)
Unskilled blue collar workers and workers without mention of skill level	2794 (13.1)	26,725 (19.6)	104,250 (32.8)	121,719 (44.1)	64,184 (37.4)	33,978 (38.6)	353,650 (35.0)
Persons outside the labour market	597 (2.8)	11,738 (8.6)	28,846 (9.1)	10,220 (3.7)	2221 (1.3)	522 (0.6)	54,144 (5.4)

* Point-years = years of full-time employment weighted by physical exposure level in employment industry

Table 3G.
Distribution of background variables among participants (cases and controls). All shown as percentage of total number of participants.

	Men		Women	
	Controls	Cases	Controls	Cases
	1803	986	1780	963
Age 1.1.2005	64.3 (3.5 SD)	64.3 (3.7 SD)	64.7 (2.7 SD)	64.7 (3.5 SD)
Actual BMI, (kg/m²), %				
<18.5	0.2%	0.1%	3.0%	1.6%
18.5 – <25	32.9%	22.7%	48.7%	36.3%
25 – <30	48.9%	49.7%	33.7%	39.7%
30 – <35	13.6%	19.6%	10.0%	15.6%
35+	3.0%	6.4%	2.5%	5.1%
Missing	1.3%	1.5%	2.1%	1.8%
BMI at age 25, (kg/m²), %				
<18.5	1.4%	0.3%	8.9%	4.8%
18.5 – <25	73.2%	68.6%	77.4%	75.7%
25 – <30	18.6%	22.7%	7.7%	10.1%
30 – <35	1.7%	2.6%	0.7%	2.3%
35+	0.6%	1.6%	0.2%	1.0%
Missing	4.6%	4.2%	5.1%	6.2%
Smoking (ever), %	69.4%	68.8%	49.5%	51.5%
Packyears, %				
0	34.3%	34.8%	51.2%	49.7%
1-19	25.6%	29.0%	23.5%	24.1%
20-39	20.9%	18.0%	18.2%	16.7%
40-59	13.5%	12.6%	6.1%	7.8%
60+	5.7%	5.7%	1.0%	1.8%
Sport at 25 years of age, %	51.3	56.7	44.1	49.3
Missing	3.2	2.6	3.3	5.5
Type of Sport				
Endurance sports, %	15.6	14.2	23.5	24.9
Risk/contact sport, %	17.5	23.3	10.6	13.7
Both endurance and risk/contact sport, %	17.5	20.8	8.1	9.2
Missing	5.0	4.2	8.5	8.1
Familiar occurrence	4.0%	7.4%	4.9%	8.3%
Missing	0%	0%	0%	0%
Diabetes				
Yes	10.2%	11.6%	6.9%	6.4%
Do not know	2.5%	2.6%	1.2%	2.6%
Missing	3.3%	5.5%	5.2%	7.5%
Thyroid				
Yes	1.8%	2.3%	10.1%	9.0%
Do not know	3.3%	4.0%	3.5%	3.8%
Missing	5.6%	7.0%	5.1%	7.3%

Table 3G continued

	Men		Women	
	Controls	Cases	Controls	Cases
	1803	986	1780	963
Rheumatoid Arthritis				
Yes	8.2%	15.8%	7.0%	11.9%
Do not know	6.9%	9.7%	6.7%	8.8%
Missing	4.6%	5.1%	4.7%	6.4%
Osteoporosis				
Yes	1.7%	2.3%	8.9%	10.9%
Do not know	4.4%	6.7%	11.0%	11.8%
Missing	5.3%	7.3%	4.3%	5.9%
Pain at all (ex. hip)	71.3%	78.0%	77.8%	81.9%
Missing	1.3%	3.1%	1.5%	3.2%
Pain hip	26.1%	55.8%	28.9%	56.9%
Missing	7.9%	4.8%	11.1%	9.3%
Fracture lower extremity	14.2%	19.5%	11.3%	17.2%
Missing	0%	0%	0%	0%
General Health (dikotom)				
Good (or better)	80.0%	74.9%	77.1%	69.0%
Bad	14.8%	20.0%	16.5%	25.4%
Missing	5.2%	5.1%	6.4%	5.6%
Educational Level				
None	12.0%	16.3%	19.6%	17.6%
Courses	8.8%	12.4%	7.2%	9.1%
Vocational training	49.4%	46.0%	31.0%	32.0%
<2 years	3.4%	2.5%	12.7%	14.1%
2-4 years	14.3%	13.6%	26.0%	24.0%
>4 years	11.7%	8.6%	3.3%	3.0%
Missing	0.4%	0.5%	0.3%	0.2%

Table 4G.
Distribution of participants according to cumulative exposure

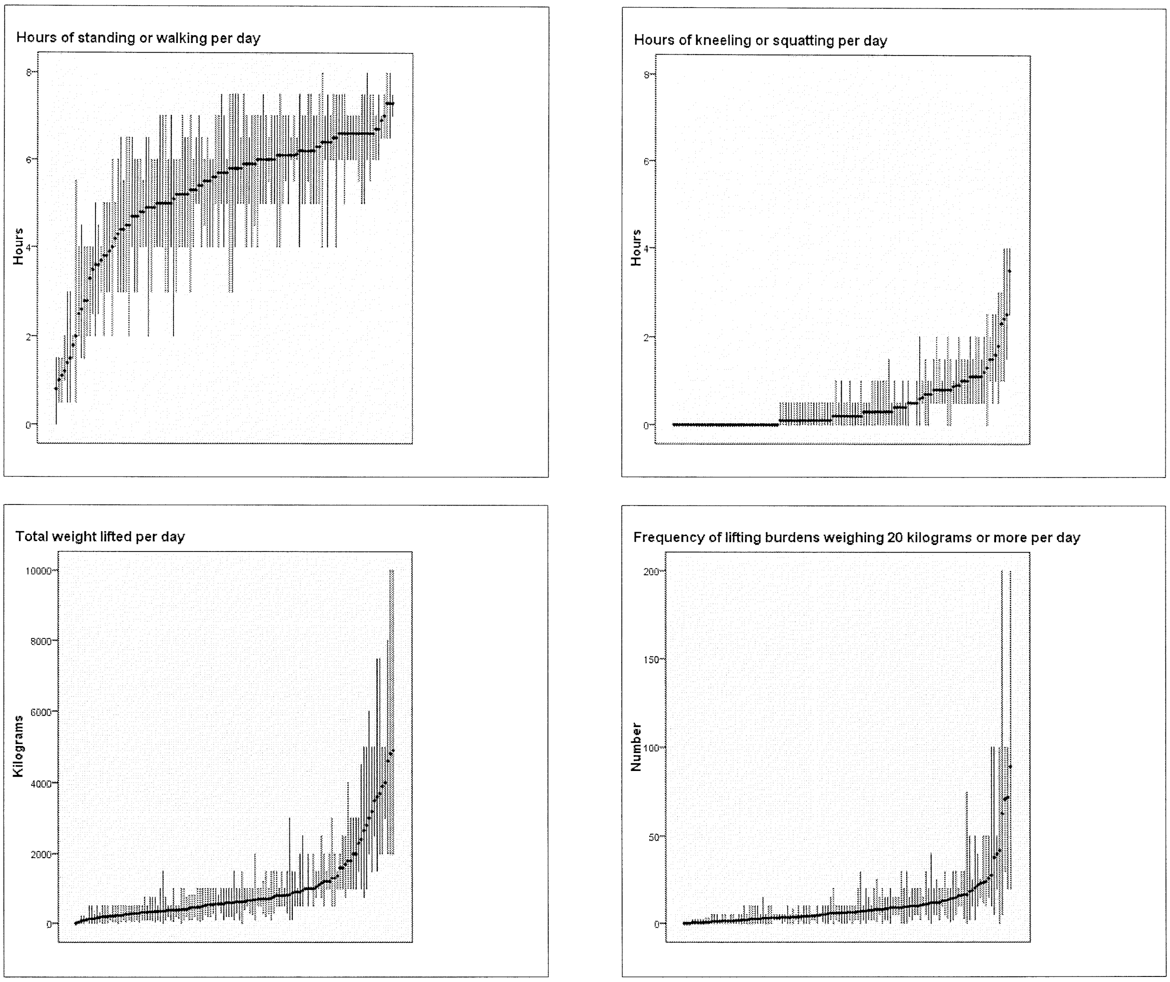
	Men		Women	
	Controls	Cases	Controls	Cases
	1803	986	1780	963
Cumulative exposure				
Standing-years				
0	43.4%	40.5%	57.1%	55.4%
>0 – 4	6.8%	7.6%	2.9%	2.6%
5 – 9	8.3%	9.1%	2.4%	2.5%
10 – 14	7.4%	8.6%	6.9%	8.2%
15 – 19	10.2%	10.9%	12.7%	12.2%
20+	21.6%	21.3%	15.6%	17.2%
Missing	2.2%	2.0%	2.5%	1.9%
Vibration-years				
0	85.6%	81.6%	93.9%	94.6%
>0 – 9	6.7%	8.8%	3.1%	3.11%
10+	5.5%	7.3%	0.5%	0.4%
Missing	2.2%	2.0%	2.5%	1.9%
Ton-years				
0	43.4%	40.5%	57.1%	55.4%
>0 – 9	18.6%	16.9%	15.3%	17.6%
10 – 29	20.5%	19.8%	23.5%	23.1%
30 – 49	8.4%	12.4%	0.7%	0.6%
50+	6.8%	8.5%	1.0%	1.4%
Missing	2.2%	2.0%	2.5%	1.9%
Lifting-years				
0	43.7%	40.8%	57.5%	55.7%
>0 – 9	17.6%	14.2%	17.9%	18.7%
10 – 29	25.5%	27.1%	20.0%	21.4%
30 – 49	7.4%	12.0%	1.7%	1.4%
50+	3.7%	4.0%	0.5%	0.9%
Missing	2.2%	2.0%	2.5%	1.9%

H. Assessment range plot

Figure 1H.

Range of individual assessments among experts for four of the exposure variables in the job exposure matrix, shown with ascending mean and range from minimum to maximum assessment per HEG.

● = mean for HEG, | = range of assessment



Papers I - III

Paper I

A job exposure matrix based on expert ratings for use in general population studies of primary hip and knee osteoarthritis in relation to physical work loads

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ABSTRACT

Objectives: To develop a job exposure matrix (JEM) cross-tabulating work related physical loads to the lower extremities with all relevant occupational titles in the International Standard Classification of Occupations (ISCO). The intention was to enable population studies of risk of hip and knee osteoarthritis using independent exposure assessments.

Methods: A total of 121 homogeneous exposure groups (HEG) were constructed comprising all Danish ISCO occupational titles. Each HEG was allocated the mean score of 5 experts' ratings of daily duration (hours) of: standing/walking , sitting, kneeling/squatting, and whole-body vibration. Total weight lifted per day (kg) and frequency of lifting burdens weighing 20 kg or more were assessed as well. Differences between mean scores and each individual expert's ratings were plotted to evaluate systematic over- or underreporting by any one of the experts. Two external experts checked their agreement with the rankings of HEGs based on mean scores.

Results: A two-dimensional JEM of physical work loads to the lower extremities covering all relevant Danish ISCO codes was constructed and reported with English ISCO codes. Experts showed considerable variation in their assessments although no single expert rated exposures systematically above or below the mean scores. The two external experts agreed on 707 of 726 rankings according to experts' mean.

Conclusion: A JEM based on expert ratings of exposures in HEGs was established. Experts showed considerable variation in their scores, but ranking of HEG based on mean scores, was in accordance with the opinion of external experts. Thus, the JEM will be suitable for specific exposure-response analysis, although the absolute values should be further validated.

INTRODUCTION

Primary hip and knee osteoarthritis (OA) are common musculoskeletal disorders, not just in older age groups but also in the working age population.(1;2) These disorders constitute the main indications for total joint replacement surgery.(3) Recent reviews have concluded that there is evidence of a causal relationship between occupational activities and primary OA of the hip and knee, although important limitations still exist, particularly due to modest quality of exposure assessment.(4-6) For primary OA of the hip and knee consistent exposure-response relations remain to be established.(5;6). In several studies exposure assessment has relied on job titles alone (7;8) or – at least in one study – crudely classified by the researchers as having low, intermediate or high physical exposures to the lower extremity.(9) Based on results of such studies, it is difficult to infer which generic exposures are harmful(4) and impossible to distinguish between safe and hazardous levels of exposures.

Available methods for quantitative assessment of generic physical exposures include expert ratings, self-reports, systematic observations, and direct technical measurements.(10) Self-reported physical exposures have unique advantages for a number of applications (11) and have been widely used even in recent studies.(12) However, self-reported exposures entail validity problems to the extent that individuals with pain overestimate their exposures leading to inflated estimates of exposure-response relations.(13) This source of bias is of major concern in cross-sectional and case-control studies of symptomatic OA. It may also be a problem in prospective longitudinal studies because patients may have endured gradually increasing joint symptoms for several years before they are diagnosed with primary hip or knee OA. Thus, the evidence-base for a causal relationship between symptomatic primary knee and hip OA and occupational physical exposures would be enhanced by studies (preferably longitudinal studies) using quantitative measures of generic exposures that are assessed independently of the musculoskeletal symptom status of the individual.

In general population studies, systematic observations and direct technical measurements are resource demanding, even if the methods are only applied to small subsets of the study population, and relevant equipment may not exist. To our knowledge, these methods have not been used in studies on primary hip OA. Observations have been used in studies of a few selected occupations with radiographic knee OA (irrespective of symptoms) as the outcome.(14-16) Direct technical measurements have been used in a study comparing two occupational groups with respect to primary knee OA defined clinically and radiographically.(17) Retrospective exposure assessment is a special challenge (18) and for this purpose expert ratings may be the best method available.(19) Expert ratings may be used either on a case-by-case basis (20) or as a means of constructing a job exposure matrix (JEM).(19)

A JEM is a feasible way to obtain independent exposure estimates based on job titles.(21;22). JEMs have proved valuable in occupational epidemiology,(23;24) but physical exposures have rarely been included.(21;25;26) An ambitious Finnish general population JEM, covered physical exposures in addition to psychosocial and other exposures. Physical exposures were scored (0-1 or 0-2),(21) but the JEM did not provide quantitative estimates that could be used to establish thresholds for hazardous exposures. For upper limb exposures, the first steps have been taken to construct general population JEMs based on direct technical measurements.(27;28)

We are aware of one general population JEM focussing on exposures to the lower limbs. This JEM was based on expert ratings of six physical exposures with respect to proportions of the working day.(25) The researchers were restricted by the fact that the 40 job groups were fixed entities developed for other purposes.(29) Hence, the job groups were often inhomogeneous as regards physical exposures to the lower limbs, e.g. one of the groups contained both writers and athletes. This meant that some of the jobs were grouped in a way that would obscure their impact.(19;30) JEMs have the drawback that they do not usually take into account the variability of exposures within occupational classes, and this misclassification of exposures tends to bias observed risk estimates towards unity.(31) On the other hand, if associations between exposures to the lower limbs and risk of hip and knee replacement surgery can be documented in studies using a JEM approach, this will profoundly corroborate the evidence from previous studies relying on self-reported exposures.

In this paper we document and present a new two-dimensional JEM (23) with job groups including all currently used occupational titles in the Danish version of the International Standard Classification of Occupations (D-ISCO 88) (32) on one axis and expert ratings of six specific physical exposures to the lower extremities on the other. Ideally, assessment of occupational exposures should reflect what is known or suspected about pathogenic mechanisms including cumulative effects, and the whole time window of relevant exposure should be covered.(33) We started from associations observed in epidemiological studies and focussed on standing/walking,(34) whole-body vibration,(35) kneeling/squatting,(14) total weight lifted per day,(5;6) and frequency of lifting burdens weighing 20 kg or more.(36)

Our aim was to provide independent exposure estimates for use in population studies on the influence of cumulative physical exposures on risk of primary hip and knee OA leading to total joint replacement. Our hope is that the JEM will prove useful not only in studies of lower limb OA, but also in research into the work-relatedness low back pain, inguinal hernias, and negative pregnancy outcomes.

METHODS

Screening of occupational titles

As our starting point we took the total list of 2227 different occupational titles that are divided into 353 D-ISCO codes in D-ISCO 88.(32) D-ISCO 88 is slightly different from the international version (37) - some English occupational titles do not occur in the Danish version and some Danish occupational titles have no counterpart in the international version. It is worth noting that some occupational titles have differing codes in the two versions, for instance "furniture mover" has code number 9330 in D-ISCO 88 and 9333 in the international version, and "cutter, fish" has code number 8271 in D-ISCO 88 and 7411 in the international version. We report our JEM with international occupational titles and classification codes, where possible.

TR screened the list to exclude obsolete or very rare titles and to identify occupations with minimal exposures to the lower limbs. To be considered more than minimally exposed, at least one of the following exposures had to be present in the job: standing/walking at least six hours a day, sitting more than six hours a day, kneeling/squatting more than half an hour a day, exposure to whole body vibration more than two hours a day, lifting more than two tons a day or lifting burdens weighing 20 kg, or more, at least 10 times a day. Cut-off levels were chosen according to earlier studies. For sitting, we defined the cut-off level higher than earlier studies, prioritizing specificity rather than sensitivity. Driving tractors and heavy machinery (e.g. road rollers and excavators) was considered to entail whole body vibration, whereas riding cars, lorries, trucks and trains was not. PF and SWS checked TR's decisions and the few disagreements were settled in consensus.

Establishing homogeneous exposure groups

Exposed occupational titles were collapsed into groups with expected homogeneous exposure patterns (homogeneous exposure groups, HEGs) with respect to all exposures that we intended to assess.(38;39) D-ISCO 88 groups were split up if their exposures were judged to differ, e.g. "barkeeper" and "general manager, camping site" were classified in different groups. On the other hand, several different D-ISCO 88 codes could be categorised in the same HEG. The grouping of occupational titles was discussed in the exposure assessment panel that was constituted by four occupational health physicians (SWS, PF, JHA, and JPH) and an MD specialising in occupational medicine, TR. Any disagreements were settled in consensus.

Expert rating of HEG exposures

The number of experts in the exposure assessment panel was chosen in accordance with recent recommendations.(40) The occupational health physicians all had at least 10 years of experience from departments of occupational medicine in different areas of Denmark. All experts participated in a pilot rating of ten randomly selected HEGs, which did not lead to any adjustments of the rating process.

Each expert independently entered his/her ratings into an electronic database. For each HEG, the experts were asked to rate the mean number of hours per day spent sitting, standing/walking, kneeling/squatting, and exposed to whole-body vibration (in half-hour intervals). Standing/walking, sitting and kneeling/squatting had to add up to a full working day defined as eight hours. For lifting, the experts were asked to state the mean number of kg lifted per day, and the mean frequency of lifting burdens weighing 20 kg, or more per day. The ratings were compared and gross outliers were discussed at a panel meeting. Most disagreements arose due to misinterpretation of occupational titles and components of the jobs. After reaching a consensus on job components, two HEGs were re-evaluated. For each HEG, the means of the independent ratings were included in the JEM. In this way we aimed to synthesize the best features of panel team work/consensus ratings and independent assessments.(25;40;41)

Inter-rater agreement

We used Bland Altman plots of the differences between the means and each individual expert's ratings of the HEGs against the means to judge systematic disagreements with the same experts tending to rate above or below the mean.(42) A kappa statistic cannot be used for simultaneous comparison of more than two raters or groups of raters. Correlations between different assessment methods are affected by the amount of variability present in the variables being compared,(11) and represent degree of association, not agreement.(42)

Validity

To validate the JEM in the absence of a gold standard, we ranked the HEGs according to their mean values for each exposure variable. For standing/walking and sitting: 0-<2, 2-<4, 4-<6, 6+ hours; kneeling/squatting and whole-body vibration: 0, 0-<½, ½-<1, 1-<2, 2-<4, 4+ hours; total weight lifted: 0-<500, 500-<1000, 1000-<2000, 2000-<4000, 4000+ kg; daily frequency of lifting burdens of 20 kg, or more: 0-<5, 5-<10, 10-<20, 20+. Two experts (AK, LDJ), who were not involved in the expert ratings stated if they agreed with the rankings, and suggested any adjustments.

RESULTS

We excluded 117 occupational titles that were considered rare or obsolete. A total of 1421 occupational titles were initially judged to be minimally exposed. This left 689 occupational titles that were grouped into 121 HEGs, each containing from one to 34 different occupational titles. Of the 689 Danish occupational titles only 556 could be translated into English, and 91 of the English occupational titles did not have an ISCO number. Hence, the final JEM contains 556 English occupational titles, and 157 ISCO numbers. The flow from total D-ISCO 88 to final number of HEGs is shown in Figure 1.

Table 1 depicts the mean, 10th, 50th, and 90th percentile for the six generic exposures

Table 1. Distribution of ratings of six generic exposures in 121 homogenous exposure groups, based on assessments by five experts.

Exposure	Mean	10th percentile	50th percentile	90th percentile
Standing/walking, hours/day	5.3	3.0	5.7	6.6
Sitting, hours/day	2.3	0.8	1.9	4.8
Kneeling/squatting, hours/day	0.4	0	0.2	1.1
Whole-body vibration, hours/day	0.1	0	0	0.2
Total weight lifted kg/day	955	193	590	2525
frequency of lifting burdens of ≥20 kg, times/day	10.2	1.2	6.0	21.5

To illustrate the composition of the JEM, three HEGs are shown in Appendix A. The total JEM can be obtained from the corresponding author. Some HEGs in the final JEM turned out to be less exposed than the initial cut-off points used to identify occupational titles with minimal exposures (examples not shown).

Mean and ranges of ratings are presented in Figure 2 for four of the exposure variables. The two last exposures are not shown, due to either very few exposed HEGs (whole-body vibration) or the exposure almost just mirroring standing/walking (sitting). Inspection of

Bland Altman plots did not reveal a single expert as systematically rating exposures above or below the mean (graphs not shown).

Two external experts checked the ranking of HEGs, and agreed in 707 out of the 726 original ratings (6 exposure variables for each of 121 HEGs). One of the experts suggested 10 changes (seven increases and three decreases of exposure), and the other suggested nine changes (four increases and five decreases). None of these suggestions was the same. Accordingly, we did not change the JEM.

DISCUSSION

We have developed a JEM cross-classifying 121 HEGs with six generic exposures to the lower extremities. The JEM encompasses the whole labour market in Denmark and provides quantitative exposure measures suitable for identifying exposure thresholds and for developing preventive guidelines.

We grouped occupational titles instead of D-ISCO codes that are based on skills required to fulfil tasks and duties of the jobs (37) and thus may not reflect specific exposures. More than 50% of all occupational titles were initially assessed as minimally exposed. To the extent that these groups are in fact more than zero-exposed, exposure-response relations based on the JEM will underestimate true associations. Some of the HEGs in the final JEM received one or more exposure estimates that were lower than the cut-off points used in the screening process. We kept these estimates in the JEM to reduce the risk of underestimation of associations due to misclassification of exposures that are not really minimal.

The use of probability of exposure has been proposed as a means to minimize bias due to misclassification of exposures.(43) This is meaningful in studies of chemical exposures that occur in specific occupational groups, where some group members are exposed and others are not. For physical exposures, the situation is typically different. For instance, standing or walking is widely distributed between and within occupational groups and does not occur in an on or off manner, and exposure to whole-body vibration occurs only in a few occupations, where the majority of the group members are probably exposed to some extent. Therefore, we thought that it would be more informative to provide quantitative estimates of mean exposures.

In general, exposure variation within HEGs and overlapping exposure profiles between HEGs means that exposure-response relations based on JEMs tend to be underestimated.(22;23;31) To minimise this problem, we designed the job axis of the matrix to contain as homogenous exposure groups as possible,(39) benefitting from the fact that we did not have the constraints faced by D'Souza et al.(25) Well-defined quantitative classes give better possibilities to observe unbiased exposure-response relationships. When choosing between approaches for exposure assessment, it should also be remembered that an individual (as opposed to a group based) approach is also subject to attenuation of exposure-response relations.(19)

It is a strength that our JEM is based on independent exposure assessment. Maybe the accuracy of our exposure estimates could have been improved if we had provided the experts with brief texts describing the work content of the occupational groups represented in the HEGs. (40) Such descriptive texts could also make it easier to adapt the matrix for studies of other populations. We refrained from the use of exposure vignettes because our exposure assessment panel included experienced specialists, who knew the tasks of the majority of occupational titles present in the HEGs.

As compared to observations and technical measurements, expert ratings may be (rather) inaccurate for assessing level, duration and frequency of posture, movement and exerted force. Our first priority was to rank the job groups in a valid way since this is a precondition for exploring exposure-response relations. As a next step, we could develop a framework for validating or adjusting our exposure estimates by establishing benchmarks across our range of exposures, for instance by focus group interviews with representatives of HEGs with different exposure rankings. Benchmarks could also be obtained by observations and/or direct technical measurements for selected groups.(44) On the other hand, we estimated that floor-layers are exposed to kneeling work for on average 3.5 hours/day, which is comparable to estimates based on observations and measurements,(15;17) and it seems reasonable that no job groups obtained a higher mean. We think that at large our quantitative estimates reflect true exposures quite well.

We did not use different estimates for men and women within the same occupation.(24) Women in heavily exposed jobs may actually be less exposed than their male colleagues for instance due to gender segregation of tasks within jobs. In less exposed jobs the opposite may be true for instance if males tend to work as leaders. To the extent that this is the case, the exposure contrast between jobs will be overestimated for women, which would have the effect that women would erroneously seem to be less affected by heavy exposures than men would. A perspective for improvement of the JEM could be to provide gender specific estimates for selected groups. However, the Danish labour market is to a large extent gender segregated so that men and women work in different jobs, which means that the practical significance of such an effort may be limited.

Our JEM is available with all occupational titles in the different HEGs and corresponding exposure estimates. In this way, it will be possible to update specific exposure estimates as new knowledge is obtained, and other researchers will be able to modify the JEM for use in different study populations. Until more accurate and precise methods for exposure assessment have been developed for use in large scale population studies of hip and knee OA, we find it promising to explore the avenue of a JEM approach based on expert ratings of physical exposures.

CONCLUSION

We have developed a JEM for use in general population studies of primary hip and knee OA with a potential for use in studies of other health outcomes and in other countries with an industry composition similar to the Danish. We do not see the matrix as a fixed entity, but an entity to be developed and updated, when more knowledge becomes available.

ACKNOWLEDGEMENTS

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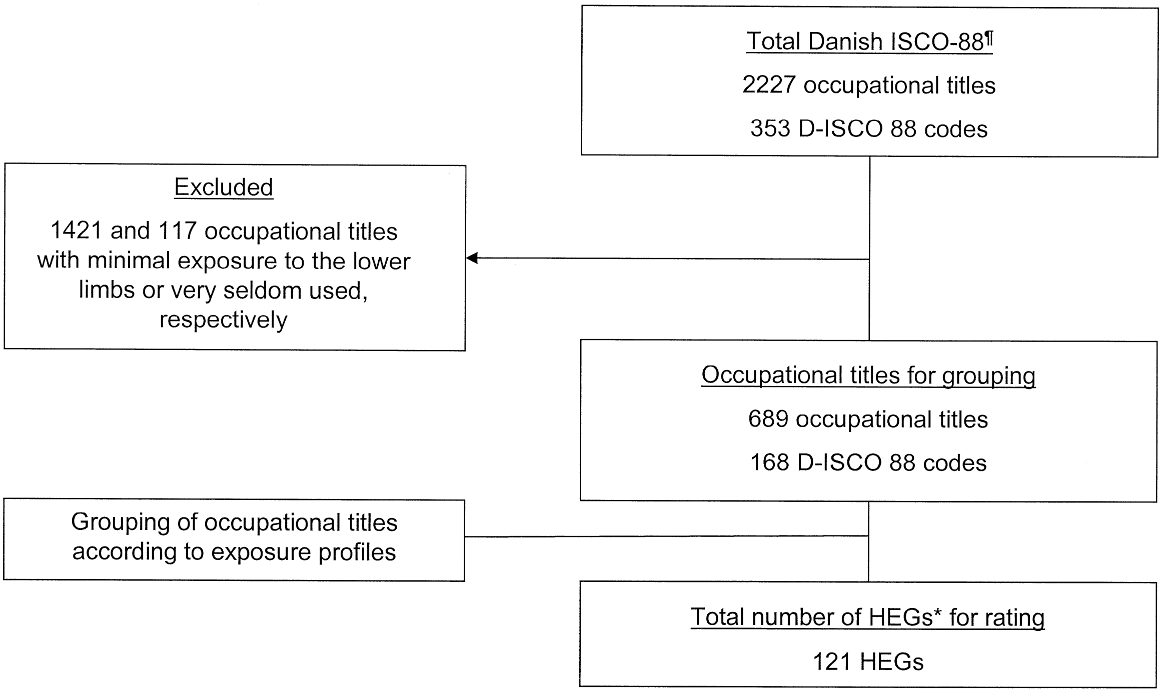
Figure 1.

The flow of occupational titles and related ISCO codes to create the final 121 homogeneous exposure groups to be assessed.



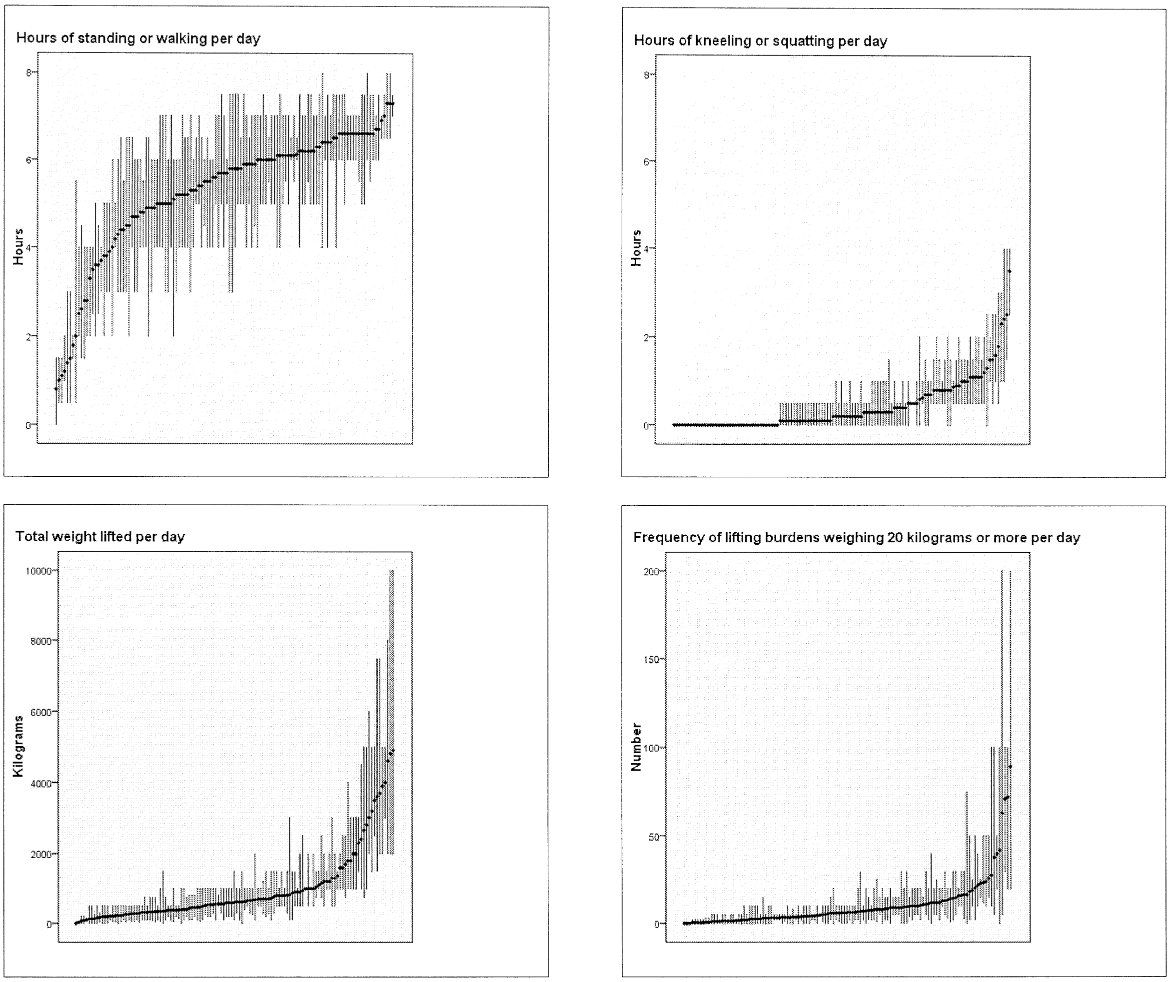
¶ISCO-88: Danish version of the International Standard classification of Occupation

*HEG: homogeneous exposure group

Figure 2.

Range of individual assessments among experts for four of the exposure variables in the job exposure matrix, shown with ascending mean and range from minimum to maximum assessment per HEG.

● = mean for HEG, | = range of assessment



APPENDIX A

Three of homogeneous exposure groups (HEG) from the job exposure matrix. The full matrix can be obtained from the corresponding author.

HEG number	DST no*	ISCO†	Occupational titles within HEG	Exposure assessments (mean scores by five experts) for an eight hours working day					
				Standing (hours/day)	Sitting (hours/day)	Kneeling (hours/day)	Whole-body vibration (hours/day)	Total weight lifted kg/day	Frequency of lifting burdens of ≥20 kg/day
1	1	1311	General manager, agriculture (except those in nurseries and green houses)	4.8	3.0	0.2	1.1	900	9.6
		6111	Farm worker, skilled/potato						
		6112	Farmer, fruit						
		6121	Farmer, horse breeding; farm worker						
		6122	Farmer, poultry/hatching and breeding; breeder, poultry						
		6129	Farmer, fur/non-domesticated animals						
		6130	Farmer, mixed farming; farm worker, skilled/mixed farming						
		9211	Groom, stud; labourer, farm;						
		no ISCO	Farmer, fur/non-domesticated animals (mink); groom						
12	2	8231	Machine-operator, rubber; machine-operator, vulcanising/rubber goods	6.7	1.1	0.2	0	1150	6.4
48	3	8161	Operator, generator/electric power	4	3.8	0.2	0	380	2.4
		8162	Operator, boiler plant/steam						

*Numbers according to the 9-grouping of industries defined by Statistics Denmark (DST) 1 – Agriculture, fishing and quarrying, 2 – Manufacturing, 3 – Electricity, gas and water supply

† ISCO codes in accordance with the International Standard Classification of Occupations

Paper II

Risk of total hip replacement due to primary osteoarthritis in relation to cumulative physical work loads: a nationwide cohort study

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Word count: 3630
Keywords: Osteoarthritis, hip, risk assessment, industry exposure matrix

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ABSTRACT

Objective: The aim of this study was to investigate the risk of total hip replacement (THR) due to primary osteoarthritis in relation to cumulative physical work load.

Methods: We conducted a register-based cohort study of the Danish working population. For each individual, we constructed a cumulative estimate of physical work load for the entire working life after 1964 using information on employment history and an industry exposure matrix. The matrix provided a score of physical work load in each of 111 industries on a three point scale, 0 (minimal load), 1 (moderate load) and 2 (high load). The score was used to weight each year of employment. Cumulative exposure estimates were expressed as 'point-years' corresponding to the pack-year concept used for cumulative tobacco consumption. Information on THR was retrieved from the National Patient Registry during an 11 year follow-up period. Discrete survival analysis was used to calculate risk estimates, adjusting for age, socioeconomic status and county of residence.

Results: Exposures ranged from 0 to 94 point-years. For men, an exposure-response relation was observed (HR 1.02, 95% CI 1.02 – 1.03 for an increase of five point-years) with a threshold of 16-20 point-years. The threshold level could be obtained by for instance 8-10 years of employment in industries with high physical work load. For women no exposure-response relation was found.

Conclusion: For men there was a slightly increased risk of THR with increasing cumulative physical load to the lower extremities, and a threshold was observed. For women no exposure-response relation was observed. The observed risk profile implied that amongst men with at least 16 point-years, a total of around 1140 cases of THR were attributable to physical work load, corresponding to 16%. Thus, our findings suggested that at the population level, physical work load has a non-negligible impact on risk of THR among men.

INTRODUCTION

Primary osteoarthritis (OA) is the most common joint disorder in the world.(1) All joints are susceptible, and risk factors differ between joints.(2) It has been estimated that work related OA accounts for about 9% of the total costs for all OA,(3) showing that work related OA has a high impact, not just for the individual, but also in an economical perspective. In the US alone, the combined number of knee and hip joint replacements performed is in excess of 350,000 annually.(1)

Pain and disability are the most important indications for surgical intervention.(4) Primary OA of the hip is a major cause of morbidity and disability in the elderly, and the problem will increase with the aging of the populations in Western societies.(5) The working age population is also affected.(6) According to the Danish Hip Arthroplasty Register, 50.8% of all hip arthroplasty operations in 2007 were performed before the age of 70, 77.6% were due to primary OA (approximately 3030 operations), and 58.2% were performed in women.(7) THR may be seen as an indicator of end stage disease of primary OA of the hip.(8) End stage OA is of public health concern in Western societies with influence on physical capacity among working age people as well among the elderly. Although THR is considered an effective and safe treatment, complications occur in relation to operations. In Denmark, 21% of THR patients had blood transfusions within the first seven days after THR, and within ten years 5-10% underwent revision.(7) Perioperative mortality has been reported to be around 0.5% within three months in patient groups with a mean age in their mid sixties.(9).

Established risk factors for OA and THR include age, a high body mass index (BMI),(10-12) hip injuries and constitutional predispositions.(13)

It is a longstanding theory that mechanical wear and tear through life is a contributing cause of primary OA.(14) Several reviews have concluded that there is moderate to strong evidence of a causal relationship between primary OA of the hip and occupational work load.(5;15-17) However, these reviews have agreed that there is sparse knowledge of the amount of physical work load needed to cause hip OA because few longitudinal studies have been conducted,(10;18-23) and because exposure assessment has been inadequate. Longitudinal studies have used job titles as such(18;22) or crudely classified by the researchers into a few broad exposure groups without assessing cumulative exposures,(19;20;23) or they have used recent physical exposures assessed by self-report.(10) Self-reported exposures may exaggerate exposure-response relations to the extent that individuals with pain overestimate their exposures. From the studies just mentioned, it is not possible to determine exposure-response relations regarding cumulative exposures. Reported case-control studies generally included less than 1000 subjects. Again, some studies used job titles alone,(24) or broad exposure groups based on job titles without assessment of cumulative exposures.(25) Others relied on self-reported exposures in main job, recent job, or job 10 years prior to entry into study.(11;26-29) Exposure-response relations between amount lifted per week have been examined in two studies,(30;31) and duration of employment in different occupations has been examined in two studies of farm work, (24;32) one of which evaluated effects of cumulative exposure.(31) The last-mentioned study focussed on cumulated self-reported exposures from age 16 to age 49.

We are not aware of longitudinal studies examining risk of THR due to OA in the general population in relation to cumulative and independently assessed physical load for the entire working life.

This study was performed to evaluate the risk of THR due to primary OA in Denmark in relation to employment in industries with different levels of physical work load using nationwide registers of individual historical employments and hospital contacts. We hypothesized that increasing cumulative physical work load leads to increasing risk of THR due to primary OA and aimed to establish cumulative exposure-response relations.

METHODS

Design and population

We conducted a register based follow-up study of THR in Denmark among employed males and females. Based on data obtained from the Danish Civil Registration System (CRS) (33) in 2007, we identified all persons born in Denmark between January 1, 1925 and December 31, 1964. We excluded persons registered as claimers of "protection against inquiries in connection with scientific studies". Data were then linked with the Register of Danish Labour Market Supplementary Pension Scheme, and those who did not reach 10 years of full time employment between 1964 and 2006 were excluded together with a few persons who had distorted information on work history. Periods of self -employment are not informed by the register, which means that for instance farmers were underrepresented in our study. Based on data from CRS, we excluded those who lived in Greenland had emigrated or died before January 1, 1996 (CRS) or before reaching 10 years of full time employment. We excluded all who had received a THR between 1977 and 1995 (both years inclusive) according to data from the Danish National Patient Registry and those who had missing information of socioeconomic status (SES) in the files of Statistics Denmark (DST).

Outcome and follow-up

Outcome was defined as first THR due to primary OA in the follow up period from 1996 to 2006. Information on type and date of surgery was collected from the NPR. Until Jan 1, 1994, diagnosis was based on ICD-8 codes (osteoarthrosis coxae - 713.00) and thereafter on ICD-10 codes (arthrosis coxae primaria - M16.0, M16.1, M16.9). Surgical procedures were registered in accordance with the NOMESCO Classification of Surgical Procedures (hip replacement surgeries - KNFB20, KNFB30, KNFB40, KNFB99).(34) ICD-8 codes were used to exclude individuals, who had a hospitalisation due to primary OA before start of follow-up, as this could be expected to reflect joint surgery. During the follow-up period, only ICD-10 codes were used in the NPR.

The cohort was followed from January 1, 1996 to December 31, 2006. Individuals who reached their 10th year of full time employment between January 1, 1996 and December 31, 2006 entered the cohort at the beginning of the year when they reached these 10 years. Follow-up time was calculated from Jan 1, 1996 or from the first year after obtaining at least 10 years of employment until the date of THR due to primary OA or censoring due to 1) THR for other disorders than primary OA, 2) emigration, 3) death or 4) end of follow up by Dec 31, 2006, whichever came first.

Exposure assessment

Employment status year by year since 1964 was collected from the register of the Danish Labour Market Supplementary Pension Scheme. For each individual and for each year of employment, industry, and degree of employment (part, full, or over time) was obtained. In the register of the Danish Labour Market Supplementary Pension Scheme industry of employment is classified into 111 industry groups defined by Statistics Denmark.(35)

This information was linked to an industry exposure matrix (IEM) developed for the purpose of this study. Three of the authors (TR, SWS and PF) rated the combined physical work load to the hip in each industrial group on a three point scale, 0 (minimal load), 1 (moderate load) and 2 (high load). The exposures that were taken into consideration were: standing/walking, whole-body vibration and lifting (primarily total daily loads lifted) in terms of mean exposures. Ratings were done independently. The final ratings were reached in consensus. Examples of industries with minimal physical work load were " real estate agents etc.", "primary and secondary education", and "other financial intermediation". Industries with moderate load included "restaurants" and "hospital activities". Highly exposed industries were for instance "sewage and refuse disposal and similar", "bricklaying" , "agriculture", “manufactures of furniture” and “production of meat and meat product”. For each individual, a cumulative estimate of physical work load called ‘point-years’ was calculated as total years of employment (adjusted to full time employment) in a specific industry weighted by the corresponding score of physical work load from the IEM. This was summed up across all years of employment until end of follow-up. Thus it was possible for participants to accumulate exposure during the follow-up period. As an example, a person who worked full time for four years in an industry with high physical work load, worked part time (50%) for six years in an industry with moderate load, and finally worked more than full time (120%) for 10 years in an industry with minimal load would obtain a cumulative estimate of physical work load of 11 point-years ((4 years * 100% * 2 points) + (6 years * 50% * 1 point) + (10 years * 120% * 0 points)).

Socioeconomic status

Information on SES was gathered from Statistics Denmark. For each person SES was collected for 1980, 1986, 1996 and 2006. To obtain SES in the age span from 40-55, SES from 1980 was used for those born 1925-1935, and SES from 1986, 1996, and 2006 was used for those born 1936-1945, 1946-1955 and 1956-1964, respectively. If SES for the relevant year was missing, the nearest informative SES was used, if no earlier information was available, then later information was used.

Statistics Denmark has changed SES coding several times, and hence we had to create a common SES from three different classifications with approximately 20 groups in each. We grouped the SES from DST into five levels in the following way: group 1 included self-employed and their spouses; group 2 included top leaders in business and organisations together with highly skilled white collar workers; group 3 included other white collar workers and skilled blue collar workers; group 4 included unskilled blue collar workers and workers with unknown skill level; group 5 included persons outside the labour market.

Ethics

The study was approved by the Danish Data Protection Agency. In Denmark, research that only entails register and questionnaire based data does not need to be approved by the Committee System on Biomedical Research Ethics.

Analyses

Data was analysed by multiple logistic regression. The usage of multiple logistic regression in accordance with Richardson equals survival analysis using Cox-regression and yields hazard ratios (HRs),(36) interpretable as incidence rate ratios. For each THR, cumulative exposure estimates for the risk set (persons who were alive and being observed in the study at THR date of the case) were based on the exposure history up to the date of THR of the case. We categorised the individual numbers of point-years into six groups for men and five groups for women since high cumulative physical work load was rare among females. The following upper cut-off points were chosen: 0 (the reference group), 5, 15, 25, 35 and 90 point-years. The cut-off levels were selected based on the distribution of point-years for both genders so that we obtained exposure groups of approximately same size, while ensuring exposure contrast. The highest exposure group for women had 25 point-years as cut-off level. Besides the grouped exposure variable, a continuous exposure variable was analysed with five point-year increments. Analyses were stratified for gender. Besides cumulative exposure we a priori decided to include age (continuous, with one year increments) , SES (categorized with group 1 as reference), county of residence, calendar year, and number of follow-up intervals (whole years) in the full model.(37) We also performed analyses with adjustment for age alone. No other variables were tried in intermediate analysis.

To be able to visually evaluate exposure-response patterns the study population was divided into the reference group, consisting of those who had always worked in an industry with a IEM score of zero, and nine exposure groups of equal sizes that were then analysed in the full model. The HRs thus obtained were plotted against the average number of point-years in each of the ten exposure groups, and a spline in 10 bands was performed. Etiologic fraction was calculated as (HR-1)/HR. Thus it is possible to calculate the fraction of cases, attributable to physical exposure. This was only done for the male part of the population.

Analyses were performed on Statistic Denmark's research platform using Stata10 SE.(38)

RESULTS

The birth cohorts comprised 2,522,349 persons (1,263,507 men and 1,258,842 women). We excluded 252,563 men and 359,293 women; see Figure 1.

A total of 1,010,944 men and 899,549 women were included in the study. The women were on average 47.6 years old at entry into the study, which was approximately one year younger than the men were. At start of follow-up the men had a higher mean cumulative physical work load (17.7 point-years) than the women (10.6 point-years). During 9,126,600 person years of follow up 8784 new cases of THR appeared amongst women, and during 10,297,402 person years of follow up 9900 new cases were recorded amongst men. Tables 1 and 2 depict the distribution of follow-up time, age at start of follow-up, number of cases and SES at age 40-55 years according to exposure groups and gender.

Women

In age adjusted analyses, all exposed groups had a lower risk of THR than the reference group (table 3). The lowered risk disappeared when controlling for SES and county of hospital. Age was the most important risk factor, yielding an increased risk of approximately 11% per year.

Men

For men the risk of THR due to primary OA increased with increasing cumulative exposure in the age adjusted analyses (table 4). In the final model, an exposure-response relationship was seen for cumulative physical work load. Again, age was a strong a risk factor.

The spline graph for men (Figure 2) indicated a threshold between 16 and 20 point-years of cumulative physical work load, with an increasing trend that levelled off after around 40 point-years. Figure 3 displays the spline graph for women; no exposure-response relation is seen.

Etiologic fraction was estimated based on the spline regression, only for men. According to the spline, HR for those with more than 16 point-years equals approximately 1.2. Thus, etiologic fraction equals 1/6 ((1.2-1)/1.2), which means that 1138 cases (1/6 out of at total of 6828 cases) can be attributed to physical work load in the three most highly exposed groups.

DISCUSSION

This study was performed to evaluate the impact of cumulative physical work loads to the lower extremities on the risk of THR in a nationwide Danish cohort comprising the working population. We showed a slight dose dependent increase in risk, reaching a maximum of a 30% increased risk for men, but not for women. For men, a threshold was suggested corresponding to 16-20 years of work in industries with moderate physical work load or 8-10 years of work in industries with high physical work load. We took advantage of national longitudinal registers to obtain individual information about THR, employment industry (year by year since 1964), duration of employment normalised to fulltime years and SES. We used a cumulative measure of exposure that summarized total number of employment years weighted by exposure scores obtained from an IEM based on expert ratings. We used expert judgement to obtain independent exposure estimates and thus avoid recall bias, which may have caused inflation bias in previous studies of THR relying on self reported exposures.(11;23;26-29) Since we had calendar year specific information on employment industry, we were able to account for transitions between industries.

We are well aware that the crude exposure assessment resulted in small exposure contrasts and non-differential misclassification both leading to an underestimation of true risks. For instance, some employees in industries with moderate or high loads may in fact have performed administrative tasks and thus should have been allocated to a group with minimal work load.

Our IEM was not gender specific. Maybe underestimation of risks was especially pronounced among women because women in industries with high exposures may be more likely than men to hold jobs with minimal physical load, e.g. office jobs. A greater tendency towards exposure misclassification for females than for males may be part of the explanation why we found an exposure-response relationship for men, but not for women. Maybe more valid exposure estimates could have been obtained if our IEM had been made for women and men separately. But then again, the Danish labour market is to a large extent gender segregated so that men and women work in different jobs, which means that the practical significance of such an effort may be limited. The risk of TRH in relation to occupational physical exposures has been analysed in other studies of female populations, some showing an increased risk(11;12;29;39) and others showing equivocal risk estimates.(23;26;40) In general, studies of female populations are few and of small sample sizes including few exposed women. Thus, it is still not clear whether the risk of THR in relation to cumulative work loads differs between men and women.

Analyses were controlled for age, SES and geographic region. Trauma to the hip joint was controlled by restriction to THR due to primary OA. Stratified analyses of men and women were performed in accordance with recent recommendations.(41) Other suspected risk factors like a high body mass index and primary OA were not taken into account, but we do not expect the distributions of these factors to be heavily skewed between industries.

Among men the risk of THR was reduced in the lower SES groups. The highest SES group included self employed with physical work exposures, e.g. farmers and other owners of small enterprises. Their exposures may be underestimated since years as self-employed are not informed by the register of the Danish Labour Market Supplementary Pension Scheme. There seemed to be a correlation between cumulative exposure and SES at age 40 to 55. By having both variables in the same model an underestimation the effect of physical work load is possible.

Information on outcome was obtained from the NPR. It has been shown that in general there is a very good agreement between medical records and registered information on surgical interventions.(42) We had no information on THR prior to the establishment of NPR in 1977, but THR was uncommon until the late 1970's. Thus, we do not have reason to suspect misclassification of the outcome. In the literature, different outcome criteria have been used, namely radiographic OA,(11;18;25;27;28;30;32;43;44) clinical OA,(19;40;45;46) being on a waiting list for THR(26;29) and receiving a THR or being hospitalised due to primary OA.(20-24;31;39)

We used THR due to primary OA as outcome measure because the stage of OA normally leading to THR is of public health concern with respect to chronic pain and disability, low but inneglectable risks of complications in relation to treatment, and need of a new replacement surgery in 5-10 % within 10 years. Valid information on THR can be obtained from Danish registers. However, the choice of THR as an indicator of primary hip OA has been questioned since THR indicates end stage disease.(8) Moreover, results obtained from THR-studies do not clearly distinguish between influences on the disease process and aggravation of symptoms. Studies of OA based on radiographic screenings irrespective of symptoms may be a way of separating these possible effects of exposure. On the other hand, radiographically defined OA cannot be directly interpreted in terms of symptomatic disease and need for THR(47).

Compared to other studies of THR,(10;31;39) we found somewhat lower risk estimates. In a study that used self-reported levels of activity (four levels), an exposure-response relation was indicated for both men and women.(10) For women, only the highest exposure level yielded a statistically significant OR, while all three levels above sedentary did so for men.(10) In a study of men, an increased risk of THR was reported with increasing static and dynamic hip exposures, and with increasing amount of heavy lifting.(31) The relationship between cumulative physical exposures and THR was evaluated among women showing an increasing risk with increasing exposure to standing and heavy lifting.(39) However, the study size was small, and the results were not statistically significant. Occupational titles were not related to risk of THR, when studying male Swedish construction workers,(21) but this may at least partly be explained by limited exposure contrast. For high levels of whole-body vibration, no increased risk was observed among men.(20) In a Swedish cohort study, an increased risk was found for men with expert assessed heavy work according to occupational , and a similar tendency was seen for women .(23) Our results supported earlier findings of increased risk of THR with increasing physical/cumulative exposures for men.(10;23;31)

When studying occupational exposures, many studies have concentrated on specific industries or jobs. The present study comprised the Danish working population with at least ten years of full-time employment across industries. We think that the results can be generalized to working populations in countries with similar industry specific work loads. We were not able to disentangle the importance of specific physical exposures. In a case-control study (study III) to extend the findings of the present study, we will obtain self-reported job histories that can be combined with a job exposure matrix containing specific physical exposures, and benefit from better information on other probable risk factors.

In spite of the fact that all sources of bias in the present study would bias risk estimates towards unity, we did find higher risks with increasing cumulative physical work loads among men, which provides quite strong evidence of the existence of an exposure-response relation.

CONCLUSION

For men, this study showed a slight dose dependent relationship between risk of primary hip OA leading to THR and increasing cumulative physical load to the lower extremities during working life. Results indicated a threshold of around 16-20 “point-years”, which could be obtained by e.g. 8-10 years of employment in an industry with high exposures. A total of about 1140 cases were attributable to physical load in the three highest exposure groups corresponding to 16% of exposed cases. For women, there was no change in risk with increasing cumulative physical work load, which may be partly explained by a larger degree of exposure misclassification among women. From a public health perspective, there is a potential for prevention, especially for men.

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Table 1.
Descriptive information on the distribution of follow-up time, number of cases, age at start of fololw-up, and socioeconomic status at the age 40-55 accoding to cumulative exposure groups for women.

	Cumulative exposure (point-years)*					
	0	>0 – 5	6 – 15	16 – 25	26 +	Total
Follow-up (years)	323,233	2,110,311	3,396,281	2,162,062	1,134,723	9,126,600
Cases	515	1720	3159	2109	1281	8784
Age in years (SD)	51.5 (11.4)	46.4 (9.4)	47.3 (10.0)	50.2 (9.3)	53.0 (8.3)	48.2 (9.9)
Socioeconomic status at age 40-55, number (%)						
Self-employed and their spouses	956 (2.7)	10,549 (4.3)	23,773 (6.3)	5,361 (3.0)	863 (1.4)	41,502 (4.6)
Top leaders in business and organisations and highly skilled white collar workers	1571 (4.3)	7867 (3.2)	8445 (2.2)	4841 (2.7)	2542 (4.2)	25,266 (2.8)
White collar workers and skilled blue collar workers	18,513 (52.0)	114,437 (46.4)	149,997 (39.8)	82,616 (46.0)	31,471 (52.0)	397,034 (44.1)
Unskilled blue collar workers and workers without mention of skill level	12,778 (35.9)	86,238 (35.0)	160,224 (42.5)	80,530 (44.8)	24,703 (40.8)	364,473 (40.5)
Persons outside the labour market	1817 (5.1)	27,446 (11.1)	34,711 (9.2)	6355 (3.5)	945 (1.6)	71,274 (7.9)

* Point-years = years of full-time employment weighted by score of physical work load in employment industry

Table 2.
Descriptive information on the distribution of follow-up time, number of cases, age at start of follow-up, and socioeconomic status at the age 40-55 according to cumulative exposure groups for men.

	Cumulative exposure (point-years)*						
	0	>0 – 5	6 – 15	16 – 25	26 – 35	36+	Total
Follow-up (years)	186,236	1,146,384	2,617,028	2,748,192	2,090,511	1,509,051	10,297,402
Cases	242	755	2075	2447	2335	2046	9990
Age in years (SD)	55.6 (11.5)	46.0 (9.1)	46.3 (10.5)	48.6 (10.5)	53.5 (9.0)	55.7 (7.6)	49.1 (10.5)
Socioeconomic status at age 40-55, number (%)							
Self-employed and their spouses	1121 (5.2)	11,187 (8.2)	48,239 (15.2)	26,885 (9.8)	7951 (4.6)	2694 (3.1)	98,077 (9.7)
Top leaders in business and organisations and highly skilled white collar workers	4843 (22.6)	16,928 (12.4)	29,149 (9.2)	27,229 (9.9)	22,738 (13.2)	11,697 (13.3)	112,584 (11.1)
White collar workers and skilled blue collar workers	12,052 (56.3)	69,699 (51.2)	107,004 (33.7)	89,793 (32.6)	74,701 (43.5)	39,240 (44.5)	392,489 (38.8)
Unskilled blue collar workers and workers without mention of skill level	2794 (13.1)	26,725 (19.6)	104,250 (32.8)	121,719 (44.1)	64,184 (37.4)	33,978 (38.6)	353,650 (35.0)
Persons outside the labour market	597 (2.8)	11,738 (8.6)	28,846 (9.1)	10,220 (3.7)	2221 (1.3)	522 (0.6)	54,144 (5.4)

* Point-years = years of full-time employment weighted by physical exposure level in employment industry

Table 3.
Risk estimates of total hip replacement due to primary osteoarthritis for men obtained by discrete survival analysis

Exposure	Hazard ratio		95% CI
	Age Adjusted#	Adjusted*	
Cumulative exposure (point-years)¶			
Reference∫	1.00	1.00	
>0 – 5	1.00	0.96	0.86 – 1.06
>5 – 15	1.00	0.96	0.87 – 1.05
>15 – 25	0.98	0.94	0.85 – 1.04
>25	1.07	0.99	0.90 – 1.10
Continuous in 5 point-year increments	1.00	1.00	0.98 – 1 02
Age (one year continuous increments)	-	1.11	1.11 – 1.11
Socioeconomic status at age 40-55			
Self-employed and their spouses	1.00	1.00	
Top leaders in business and organisations and highly skilled white collar workers	0.81	0.85	0.73 – 1.00
White collar workers and skilled blue collar workers	0.88	0.92	0.82 – 1.02
Unskilled blue collar workers and workers without mention of skill level	0.83	0.86	0.77 – 0.96
Persons outside the labour market	1.09	1.10	0.96 – 1.26

Adjusted for age at start of follow-up
*Mutually adjusted for cumulative exposure, age, calendar year, SES, amount of follow-up and county of residence.
¶ Point-years = years of full-time employment weighted by physical exposure in industry of employment
∫ Reference: those who have never worked in an intermediate or high exposure industry

Table 4.
Risk estimates of total hip replacement due to primary osteoarthritis for men obtained by discrete survival analysis

Exposure	Hazard Ratio Age adjusted[#]	Hazard Ratio Adjusted*	95% CI
Cumulative exposure (point-years)[¶]			
Reference[∫]	1.00	1.00	
>0 – 5	1.25	1.13	0.98 – 1.31
>5 – 15	1.33	1.14	1.00 – 1.31
>15 – 25	1.38	1.19	1.04 – 1.36
>25 – 35	1.44	1.27	1.11 – 1.48
>35	1.60	1.33	1.17 – 1.53
Continuous in 5 point-year increments	1.03	1.02	1.02 – 1.03
Age (one year continuous increments)	-	1.09	1.09 – 1.09
Socioeconomic status at age 40-55			
Self-employed and their spouses	1.00	1.00	
Top leaders in business and organisations and highly skilled white collar workers	0.58	0.63	0.58 – 0.68
White collar workers and skilled blue collar workers	0.72	0.73	0.69 – 0.79
Unskilled blue collar workers and workers without mention of skill level	0.90	0.87	0.81 – 0.93
Persons outside the labour market	0.85	0.87	0.77 – 0.99

[#] Adjusted for age at start of follow-up
*Mutually adjusted for cumulative exposure, age, calendar year, SES, amount of follow-up and county of residence.
[¶] Point-years = years of full-time employment weighted by physical exposure in industry of employment
[∫] Reference: those who have never worked in an intermediate or high exposure industry

Figure 1

Flowchart from general population to study-population

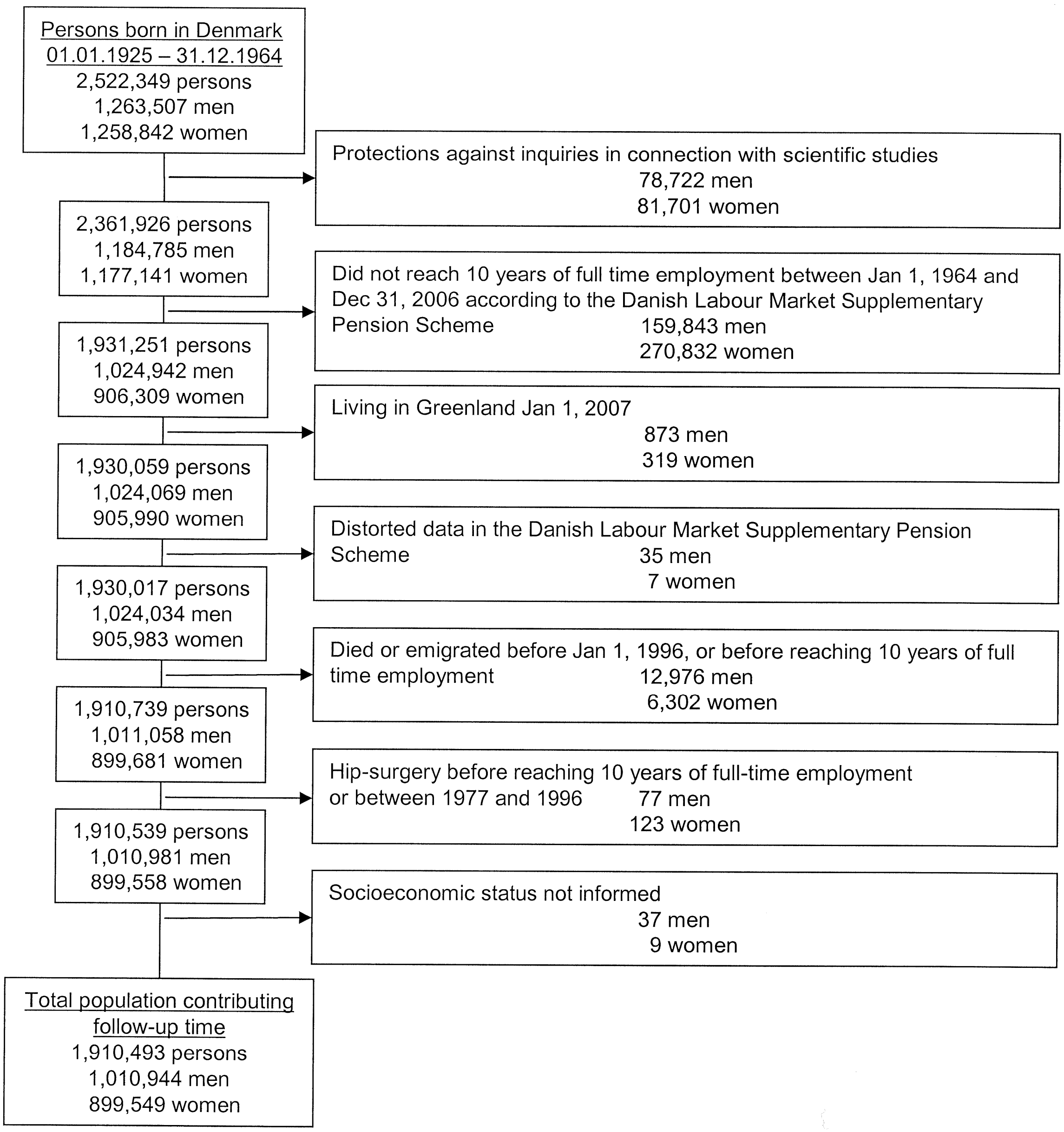


Figure 2

Spline regression for men, obtained by discrete survival analysis in 10 groups of equal size. Based on point-years*

*Years of full-time employment weighted by physical exposure in industry of employment

● = HR, ▬ = spline regression line

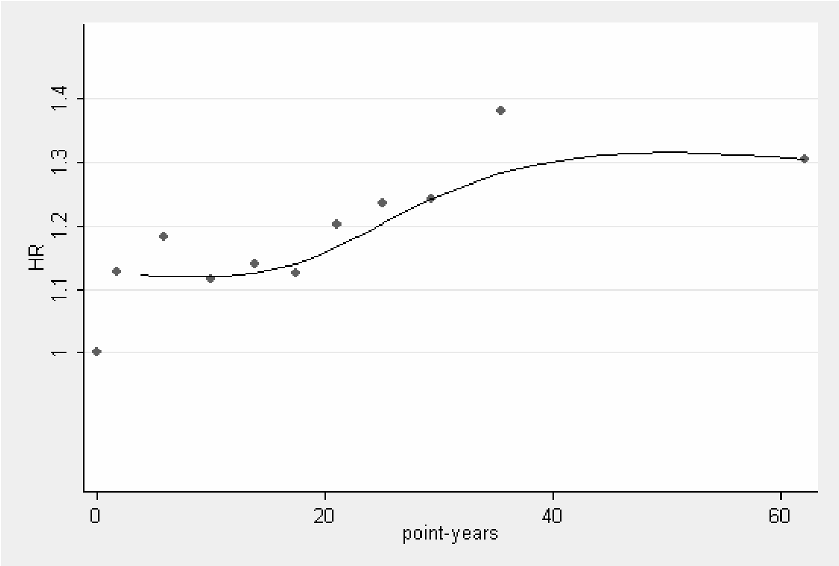
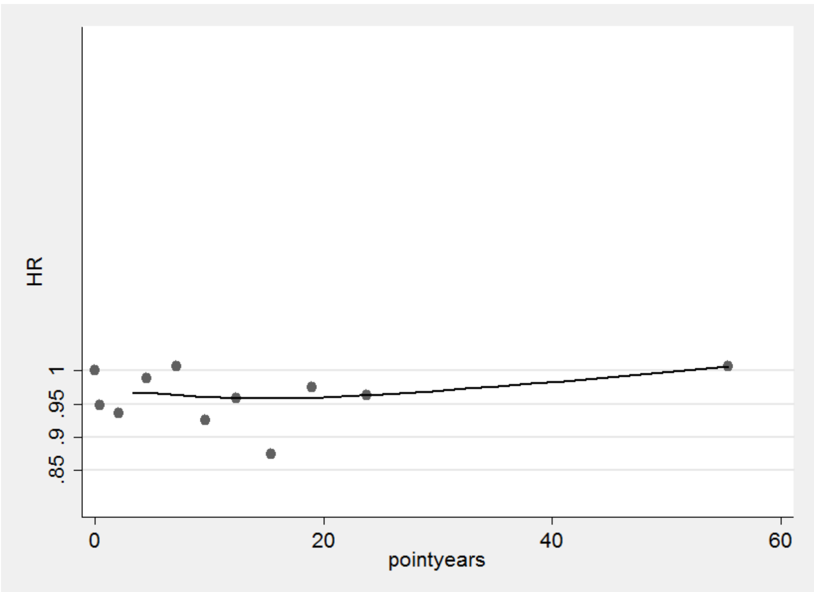


Figure 3

Spline regression for women, obtained by discrete survival analysis in 10 groups of equal size. Based on point-years*

*Years of full-time employment weighted by physical exposure in industry of employment

● = HR, ▬ = spline regression line



Paper III

Risk of total hip replacement surgery due to primary osteoarthritis in relation to specific cumulative physical work exposures: a nested case control study

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Abbreviations

CRS – Danish Civil Registration System

HEG – homogeneous exposure group

JEM – job exposure matrix

NPR – National Patient Registry

OA – osteoarthritis

THR – total hip replacement

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ABSTRACT

Objective: The aim of this study was to investigate the risk of total hip replacement (THR) surgery due to primary osteoarthritis in relation to cumulative exposure to lifting (total number of tons lifted per day and daily frequency of lifting burdens weighing at least 20 kg) and standing or walking at work.

Methods: Nested within a cohort comprising the Danish working population, we conducted a case-control study, comprising 5535 persons (49.6% women). On the date of the THR (the index date) cases were matched on gender and date of birth to two controls (risk set sampling). Data on THR in 2005 and 2006 was obtained from the Danish National Patient Registry. Cumulative exposure estimates were expressed to correspond to the pack-year concept used for cumulative tobacco consumption (standing-years, ton-years, and lifting-years). At the individual level, occupational titles were coupled to a job exposure matrix, and cumulative exposures were calculated for the 20 years leading up to the second year before the index date. Conditional logistic regression was used for analyses, controlling body mass index and other risk factors.

Results: For the entire population, an exposure-response relationship was observed for ton years (adjusted odds ratio (OR_{adj}): 1.02 (95% confidence interval (CI) 1.00 – 1.04) per five ton-years), and for lifting years (OR_{adj} 1.02, 95% CI 1.00 – 1.05 per five lifting-years). Stratified analyses revealed an increased risk for men only.

Conclusion: The results indicate a modest dose dependent increase in risk of THR in relation to cumulative lifting activities through working life among men while standing or walking at work was unrelated to risk.

INTRODUCTION

Total hip replacement (THR) is the treatment of choice for end stage disease of primary osteoarthritis (OA) of the hip.(1) During 1995 to 2007 a total of 77,408 first time THRs were reported to the Danish Hip Arthroplasty Registry of which around 80% were performed due to primary OA.(2;3) Half the operated patients were under the age of 70. The one year incidence was around 140 per 100,000 adults in 2005 to 2006.(2) End stage OA of the hip is thus an important public health problem in western societies with influence on physical capacity among working aged people as well among the elderly. THR is considered an effective and safe treatment, but complications in relation to operations occur. According to the Danish Hip Arthroplasty Register 21% of patients operated in 2006 were registered to have blood transfusions and within 10 years 5 to 10 % underwent revisions.(2) A recent review reported mortality rates of around 0.5 in 300 and an incidence of pulmonary embolism of around 1.5 in 300 among newly operated patients.(4) The studies in the review included patient groups with mean ages from 59-67 years.

Non-occupational risk factors include age, body mass index (BMI),(5) hip injury, childhood hip disorders, constitutional predispositions,(6) and maybe participation in certain sports that subject the joint to torsion, such as football, soccer, and handball.(7)

Several reviews of occupational physical exposures as risk factors for primary hip OA have concluded that there is moderate to strong evidence of a causal relationship although insufficient exposure assessment was an overall drawback.(8-10) Unsolved issues include the question of exposure-response in relation to cumulative exposures, and which specific exposures are in fact causal factors. Increased risk has been observed in specific occupations, e.g. farmers(11-13) and fishermen.(14) Several different work-related exposures have been proposed as causal factors, e.g. heavy lifting,(15-17) driving tractors and milking.(18;19) Three studies have reported an exposure-response relationship between occupational exposures and risk of THR.(17;20;21) An exposure-response relationship was shown for overall occupational loads in a study from 1991(17) and another in 2002.(20) A relationship between both standing and heavy lifting and the risk of THR has been found in yet another study.(21) A fourth study (16) also showed a relationship, but the outcome was heterogeneous comprising both THR, waiting list for THR and radiographic OA. All studies used self-reported exposures, and only the studies by Vingård(17;21) used cumulative exposures.

When using other outcome definitions than THR, exposure-response relationships have been reported for increasing occupational loads in general,(22-25) heavy lifting, (14-16;26) standing (15) and years in farming.(11;19) None of these studies used cumulative exposures.

The few studies with independent exposure assessments have not investigated specific exposures, only overall exposure. In our cohort study, we found a modest increase in risk of THR in relation to time of employment weighted by an industry specific indicator of combined physical work loads among men, but no association among women (paper II).

The aim of the present study was to examine the association between THR due to primary OA and specific cumulative physical exposures in the working environment including standing or walking, total weight lifted per day, and daily frequency of lifting burdens weighing 20 kg or more taking into account other important risk factors. We hypothesised an increasing risk of THR with increasing cumulative exposures.

METHODS

Study design

To obtain information on occupational titles and potential confounders, we performed a case control study nested in a cohort study of the Danish working population.(paper II) The cohort was identified by linking data from national registers including the National Patient Registry (NPR), (27) the Danish Civil Registration System (CRS), and the register of the Danish Labour Market Supplementary Pension Scheme. Information was linked by the unique personal identification number (28) applied to all people living in Denmark.

National registers

CRS contains information on address, date of emigration, date of death, protection against inquiries in connection with scientific studies, and protection of address.

NPR contains information on all somatic hospital admissions since 1977. All public hospitals are obliged to report to the register, and nearly complete registration is found.(27) Less complete registrations may be expected from private hospitals since registrations by these institutions was not compulsory until 2007. Since 1996 surgical procedures have been coded in accordance with the NOMESCO Classification of Surgical Procedures.(29) A good agreement between medical files and register information has been shown for THR.(12)

Since 1964 it has been mandatory for all companies in Denmark, for each employee, to pay to the Danish Labour Market Supplementary Scheme.(30) The according register contains information on industry and degree of employment for each person. Periods of self-employment are not registered.

Population

Cohort

The study focussed on working age groups, and the case-control study was nested in a cohort including all Danish men and women born between January 1, 1925 and December 31, 1964, with at least 10 years of full time employment before January 1, 2006.(paper II) For the purpose of this study, the cohort was restricted by excluding those who emigrated before January 1, 2009, died before January 1, 2009, and who had received THR before January 1, 2005. The remaining cohort was eligible for the case control sampling.

Risk set

In the cohort eligible for case control sampling, all incident cases of first time THR due to primary OA in the years 2005 and 2006. Case ascertainment was based on arthrosis coxae primaria, ICD-10 codes M16.0, M16.1, and M16.9) combined with a surgical procedure code of total hip replacement surgery, KNFB20, KNFB30, KNFB40, KNFB99. For each case, two controls were sampled, - matched on gender and date of birth - among all those in the eligible cohort who did not fulfil case criteria on the index date, being the date of THR of the case (risk set sampling). In this way a control can be sampled more than once, and even become a case later on.

A total of 4410 sets of cases and randomly sampled matched controls were generated. Among these, 2500 sets were drawn at random for the case control study.

Questionnaire data

During January through May 2009, cases and controls were sent a postal questionnaire followed by a maximum of two reminders within 7 weeks. Before mailing the questionnaires, we did an update in the CRS on vital status, protection of address, etc. We designed the questionnaire to be equally relevant for cases and controls by not mentioning THR in the information materials, and to minimise the influence of work-related exposures on decision to participate, we did not show pictures of work situations on the front page. The questionnaire asked for main job titles in specific ten year intervals from 2008 and back to 1980. Main job was explained as the job held for the longest time in each time period. Questions were also asked about height and weight at present and at the age of 25, participation in and type of sports at the age of 25, co-morbidities (diabetes, thyroid disease, rheumatoid arthritis and osteoporosis), THR in relatives, previous fractures to the lower extremities, smoking, and formal education level.

Exposure assessment

Self reported job titles were transformed into occupational titles occurring in the Danish version of the International Classification of Occupations, DISCO-88.(31) This was done by a research assistant with experience from a range of industries within the Danish labour market, and basic knowledge of jobs performed in most industries.(32) Questions of coding were settled in consensus with the authors.

The total amount of years of employment was extracted from the register of the Danish Labour Market Supplementary Pension Scheme for all participants from 1980 to 2005, both years included.

Occupational titles were linked to a newly developed two-dimensional JEM.(paper I) This JEM covers all DISCO-88 occupational titles on one axis and provides expert judgements of specified physical exposures to the lower extremities on the other. The JEM provides expert assessment of hours of exposure to standing or walking , sitting, kneeling or squatting , and whole-body vibration during an eight hour work day. Total weight lifted per day and daily frequency of lifting burdens weighing 20 kg or more were also assessed.

Cumulative measures of physical exposures were established for up to 20 years before the the year of joint replacement surgery for cases and the same year for matched controls by combining information of time in specified occupational titles with the JEM. We disregarded the last two years before surgery in this assessment to diminish the risk that a high exposure in the years just before receiving THR would influence the likelihood of being referred for surgery due to symptom aggravation by exposure. In this way THR cases appearing in 2005 and their matched controls, could accumulate exposure from 1983 to 2002 (both years included).

We generated cumulative exposure variables for hours of standing or walking, total weight lifted per day, daily frequency of lifting burdens weighing 20 kg or more, and for whole-body vibration in the same manner as pack-years are calculated from information on mean daily tobacco consumption and years of smoking to express a cumulated dose.(33) One standing-year was standardised as standing or walking 6 hours per day for one year. One vibration-year was standardised as exposure to whole-body vibration one hour per day for one year. Likewise, one ton-year was standardised as lifting one ton per day for one year, and one lifting-year as lifting objects weighing 20 kg or more at least 10 times a day for one year. The same dose of physical exposure could thus be obtained through several years with low exposure intensity or through few years with a proportionally higher exposure intensity.

Example of calculation of total exposure for standing:

*3 years in a job with 4.8 hours standing or walking per day, 10 years with 6 hours of standing or walking per day, and 7 years with 3 hours standing or walking per day = (3 years*4.8 hours/day)/6 hours/day + (10 years*6 hours/day)/6 hours/day + (7 years*3 hours/day)/6hours/day = 15.9 standing-years.*

Ethics

The study was approved by the Danish Data Protection Agency. The Danish National Committee on Biomedical Research Ethics has stated that research entailing only register- and questionnaire data does not need to be approved.

Analysis

Data was analysed with conditional logistic regression in STATA 11 with each case control set forming a separate stratum(34) in accordance with Breslow(35) Odds ratios can be interpreted as incidence rate ratios.(36) Primary explanatory variables were standing-years, ton-years, and lifting-years. According to a priori decisions, we included the following other potential risk factors: earlier fracture of lower extremities (yes/no), familiar predisposition (yes/no), type of sport performed at the age of 25 (4 categories, none, endurance, endurance and contact, contact), diabetes or thyroid disease (yes/no), smoking (pack-years), place of residence (five regions), and BMI at the age of 25 (grouped according to WHO standards, with normal as reference group).(37) Whole-body vibration was intended to be included as a primary explanatory variable, but only few participants had been exposed. Therefore, we included vibration years in the fixed set of other potential risk factors (as a continuous variable).

Formal education level was positively correlated to the exposure variables, and was omitted from the final model.

A substantial proportion of participants seemed to be unable to distinguish between rheumatoid arthritis and OA. Thus, the information on rheumatoid arthritis could not be investigated as a factor of co-morbidity.

A correlation between ton-years and lifting-years was expected, as well as correlations between standing-years and the two lifting variables. Therefore, the final models included one of the three primary explanatory variables at a time, adjusted for the above-mentioned other potential risk factors.

To evaluate the exposure-response pattern we made spline regressions on ton-years. The study population was divided in ten groups. One group with minimal exposure, and nine groups of equal size with increasing exposures. Conditional logistic regression (full model) was repeated, and ORs plotted against the average exposure value in each category. A spline in 10 bands was performed.

Analysis were done for the total study population, and also for women and men separately, in accordance with recommendations by Messing and Silverstein.(38)

RESULTS

The 2500 matched case-control sets consisted of 7445 unique persons, and of these 55 had been drawn more than once. Based on the CRS update before mailing the questionnaires, we excluded 53 unique persons, due to either death or change of willingness to participate in scientific studies (14 cases and 39 controls). We mailed a total of 7392 questionnaires, and 5495 questionnaires were returned (74.3% returned questionnaires). The final number of matched sets, available for analysis (i.e. including at least one case and one control) was 1746 (69.8%). Figure 1 shows the flow chart for the study sample for unique persons.

A minor part of those who did not participate gave a reason for this. Two women stated multiple sclerosis, three dementia/Alzheimer's disease, 12 stated other illness, and for six women their family reported that they had recently died. Among men, one stated dementia, seven stated other illness, and five had recently died.
Table 1 shows characteristics of study participants according to gender and case-status.

Table 2 displays partially adjusted and fully adjusted risk estimates in relation to physical exposures at work. There was a tendency for an overall increased risk of THR with increasing ton-years and lifting-years, for the total study population. Earlier trauma and familiar predisposition were highly associated with THR, as the two single most important other risk factors (Table 2). Type of sports and BMI were also associated with THR, and BMI showed an exposure-response relationship (data not shown).

Tables 3 and table 4 display risk estimates for women and men, respectively. Among women physical work loads showed no effect on the risk of THR after adjustment for other factors while familiar predisposition and earlier fractures to the lower extremities remained significant.

Spline regressions of fully adjusted odds ratios in relation to ton-years showed a tendency for a threshold when reaching 20 ton-years for the total study population (Figure 1). This was not seen, when analysing the two genders separately (Figures 2 & 3). For men there seemed to be a linear increase in risk until 40 ton-years, and for women, as expected, no such increase or threshold was seen.

DISCUSSION

Within the Danish working population we performed a nested age and gender matched case control study to evaluate the risk of THR in relation to specific cumulative physical exposures from work while controlling for important potential confounders. The study took advantage of independent exposure assessments.

Overall, there was a tendency for an increasing risk of THR with increasing cumulative lifting exposure whether accumulated on the basis of total weight lifted per day (ton years) or on the basis of daily frequency of lifting burdens weighing 20 kg or more (lifting years). Standing or walking at work was unrelated to the risk. Stratified analyses indicated an effect of lifting only among men.

With a proportion who participated of 75% of unique persons, and 70% useful matched groups, we do not except selection bias to be a major problem. For men participants were slightly older than non-participants, while the opposite was the case for women. More controls than cases did not participate. This was expected and a well-known phenomenon. If the reason for non-participation was related to exposure, results would be biased. To the extent that cases with high exposures were more likely to participate than controls with similar exposure, the risk would be overestimated. We expect exposure related selection into the study to be of minor importance because of the large proportions who participated both among cases and among controls and because of our efforts to ensure that the design of the questionnaire and the information material would be more appealing to highly exposed cases. A possibility of further analysis of this issue could be to investigate if there were specific industries from which subjects did not participate.

We analysed data for the total study population as a whole, and for women and men separately as recommended, (38) and found no effect of cumulative lifting activities among women when controlling for non-occupational risk factors. This result is in accordance with the results form our cohort study (paper II), and also with the result from other studies of risk of THR among women.(13;16;20;26;39) We used a newly developed JEM (paper I) to link expert assessment of specific physical exposures to individual information of occupational titles. Occupational histories are expected to obtainable in a valid way.(32) On the other hand exposure assessment, by means of a JEM, implies a risk of misclassification(40-43) that will tend to under estimate a true risk.(44) The experts did not consider differences in work loads between men and women within same job groups. Since men and women in the same job group may perform different tasks, this could lead to misclassification of exposure. However, the Danish labour market is highly gender segregated, which reduces the magnitude of this problem. Work-loads in typical female job groups like nurses aides and day care workers can be difficult to quantify. This may mean underestimation of (high) exposures, especially for women, which would lead to smaller exposure contrast, and thus attenuation of risk estimates. Our risk estimates for men were somewhat lower than those found in other studies, that all relied on self report of retrospective work loads.(17;26) Self-reported exposures may lead to overestimation of risks to the extent that persons with symptoms exaggerate their exposures. Our use of independent exposure assessment is a strength, since it reduces the likelihood of inflation bias considerably.

We disregarded exposures accumulated during the last two years before the index date to reduce the possibility that exposed cases would tend to seek care more often or earlier in the disease process due to symptom aggravation by current exposure. This would mean that an increased risk estimate could reflect symptom aggravation as well as a causal contribution to primary hip OA. A way to disentangle these possibilities could be to compare radiographic changes to evaluate whether exposed cases tend to have less pronounced radiographic changes than minimally exposed. For prevention of hip OA it certainly is important to be able to disentangle whether physical work loads throughout life time accelerate degenerative processes in the hip joint or just aggravate pain related to pre-existing degenerative alterations that have developed in relation to other causal factors. However, occupational preventive actions affecting either of these mechanisms may reduce or postpone the need of THR.

CONCLUSION

To conclude, our findings add to the evidence of a modest exposure-dependent increased risk of THR in relation to cumulative lifting through working life among men. The results do not support standing or walking at work as a risk factor.

This study of risk of THR is the first to use a JEM for assessment of specific physical exposures to the lower extremities for investigating effects of cumulative exposures

We think the JEM provides a step forward in establishing independent exposure assessment although discussions remain on problems with misclassification that also may be related to gender. The results indicate that preventive efforts should address lifting activities at work rather than standing or walking activities.

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Table 1. Distribution of background variables among participating subjects (cases and controls). All shown as percentage of total number of participating subjects

	Men		Women	
	Controls	Cases	Controls	Cases
	1803	986	1780	964
Age 1.1.2005	64.3 (3.5 SD)	64.3 (3.7 SD)	64.7 (2.7 SD)	64.7 (3.5 SD)
Actual BMI, (kg/m2), %				
<18.5	0.2	0.1	3.0	1.6
18.5 - < 25	32.9	22.7	48.7	36.3
25 - < 30	48.9	49.7	33.7	39.7
30 - < 35	13.6	19.6	10.0	15.6
35+	3.0	6.4	2.5	5.1
Missing	1.3	1.5	2.1	1.8
BMI at age 25, (kg/m2), %				
<18.5	1.4	0.3	8.9	4.8
18.5 - < 25	73.2	68.6	77.4	75.7
25 - < 30	18.6	22.7	7.7	10.1
30 - < 35	1.7	2.6	0.7	2.3
35+	0.6	1.6	0.2	1.0
Missing	4.6	4.2	5.1	6.2
Smoking (ever), %	69.4	68.8	49.5	51.5
Pack years, %				
0	34.3	34.8	51.2	49.7
1-19	25.6	29.0	23.5	24.1
20-39	20.9	18.0	18.2	16.7
40-59	13.5	12.6	6.1	7.8
60+	5.7	5.7	1.0	1.8
Missing	0	0	0	0
Sport at 25 years of age, %	51.3	56.7	44.1	49.3
Missing	3.2	2.6	3.3	5.5
Endurance sports, %	15.6	14.2	23.5	24.9
Risk/contact sport, %	17.5	23.3	10.6	13.7
Both endurance and risk/contact sport, %	17.5	20.8	8.1	9.2
Missing	5.0	4.2	8.5	8.1
Familiar occurrence,%	4.0	7.4	4.9	8.3
Missing	1.6	1.6	1.2	2.1
Diabetes, %				
Yes	10.2	11.6	6.9	6.4
Do not know	2.5	2.6	1.2	2.6
Missing	3.3	5.5	5.2	7.5
Thyroid, %				
Yes	1.8	2.3	10.1	9.0
Do not know	3.3	4.0	3.5	3.8
Missing	5.6	7.0	5.1	7.3
Fracture lower extremity, %	14.2	19.5	11.3%	17.2%

Educational Level, %				
None	12.0	16.3	19.6	17.6
Courses	8.8	12.4	7.2	9.1
Vocational training	49.4	46.0	31.0	32.0
<2 years	3.4	2.5	12.7	14.1
2-4 years	14.3	13.6	26.0	24.0
>4 years	11.7	8.6	3.3	3.0
Missing	0.4	0.5	0.3	0.2

Table 2. Risk of THR replacement in relation to cumulative exposure to physical work loads and potential confounding factors. Results from conditional logistic regression, n=3584.

Exposure	Partly adjusted odds ratio	Fully adjusted* odds ratio	95% confidence interval
Standing-years 5 years increase	1.02	1.00	0.96 – 1.04
Ton-years 5 years increase	1.03	1.02	1.00 – 1.04
Lifting-years 5 years increase	1.03	1.02	1.00 – 1.05
Smoking (per 5 pack-years)	1.00	1.00	0.98 – 1.01
Earlier trauma	1.51	1.49	1.23 – 1.80
Familiar predisposition	1.75	1.66	1.24 – 2.22
Diabetes or thyroid disease	0.78	0.68	0.53 – 0.89

* Explanatory variables are adjusted for smoking, earlier fractures, familiar predisposition, type of sports, co-morbidity, BMI at 25, whole-body vibration and geographical region. Non-occupational factors were adjusted for standing-years.

Confounders are mutually adjusted and adjusted for standing-years.

Table 3. Risk of THR replacement in relation to cumulative exposure to physical work loads and potential confounding factors. Results from conditional logistic regression analyses. Women only, n=1629.

Exposure	Partly adjusted odds ratio	Fully adjusted* odds ratio	95% confidence interval
Standing-years 5 years increase	1.03	1.00	0.94 - 1.06
Ton-years 5 years increase	1.02	0.99	0.94 - 1.04
Lifting-years 5 years increase	1.02	0.98	0.93 - 1.04
Smoking 5 pack-year	1.02	1.01	0.97 - 1.04
Earlier trauma	1.55	1.57	1.17 - 2.11
Familiar predisposition	1.72	1.75	1.15 - 2.66
Diabetes or thyroid disease	0.69	0.54	0.37 - 0.80

* Explanatory variables were adjusted for smoking, earlier fractures, familiar predisposition, type of sports, co-morbidity, BMI at 25, whole-body vibration and geographical region. Non-occupational factors were adjusted for standing-years.

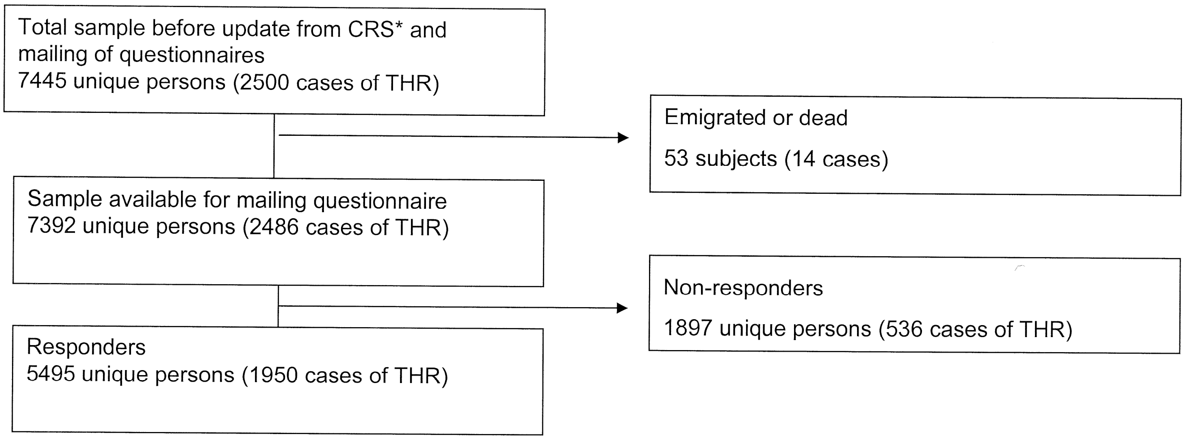
Table 4. Risk of THR replacement in relation to cumulative exposure to physical work loads and potential confounding factors. Results from conditional logistic regression. Men only, n=1955.

Exposure	Partly adjusted odds ratio	Fully adjusted* odds ratio	95% confidence interval
Standing-years 5 years increase	1.01	1.00	0.95 - 1.05
Ton-years 5 years increase	1.03	1.03	1.01 - 1.06
Lifting-years 5 years increase	1.04	1.04	1.01 - 1.07
Smoking 5 pack-year	0.99	0.99	0.97 - 1.01
Earlier trauma	1.48	1.40	1.09 - 1.80
Familiar predisposition	1.79	1.64	1.09 - 2.46
Diabetes or thyroid disease	0.86	0.77	0.54 - 1.10

* Explanatory variables were adjusted for smoking, earlier fractures, familiar predisposition, type of sports, co-morbidity, BMI at 25, whole-body vibration and geographical region. Non-occupational were adjusted for standing-years.

Figure 1

Flowchart of unique persons from sampling to participation.



* Civil Registration System

Figure 2

Spline regression (ton-years*) for total case-control population

*Ton-years: number of years with lifting five tons per day

● = OR, ▬ = spline regression line

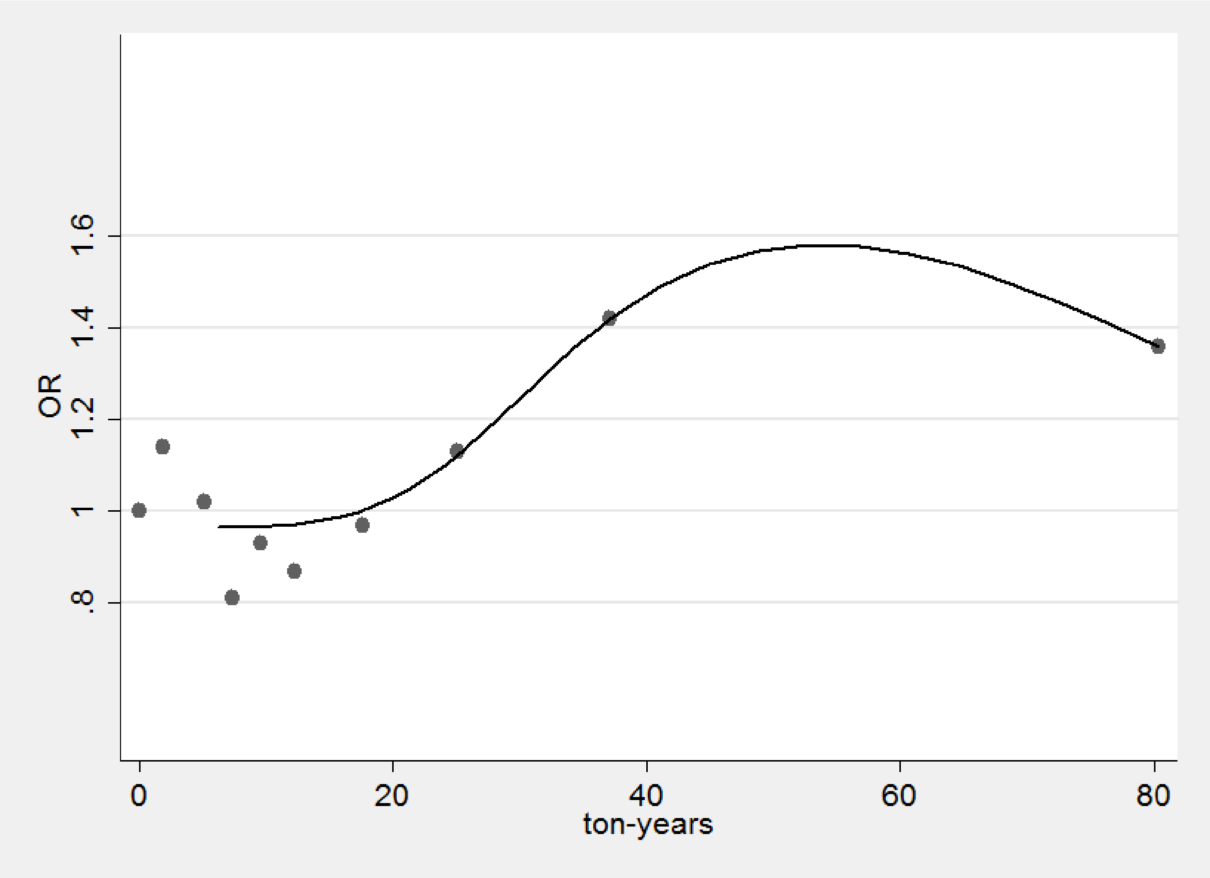


Figure 3

Spline regression (ton-years*) for men

*Ton-years: number of years with lifting five tons per day

● = OR, ▬ = spline regression line

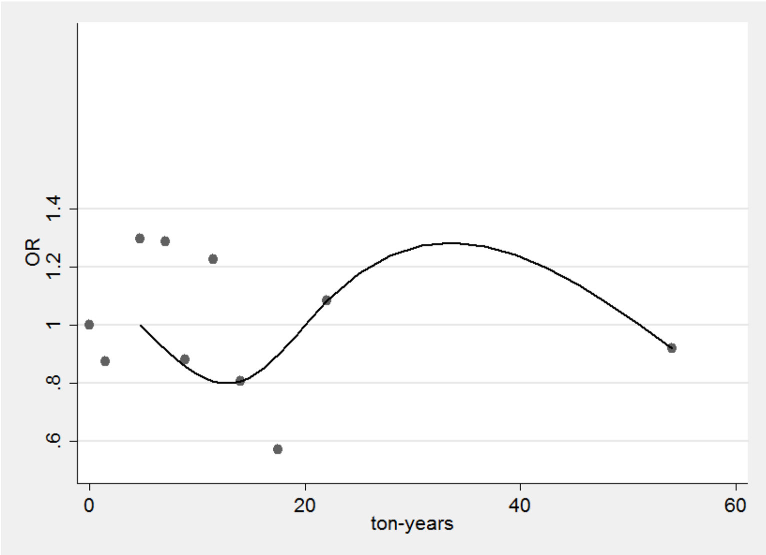


Figure 4

Spline regression (ton-years*) for women

*Ton-years: number of years with lifting five tons per day

● = OR, ▬ = spline regression line