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Study protocol: Heavy lifting at work and risk of retinal detachment

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Background

An explorative case control study [Mattioli et al. 2008] suggests that ñheavy occupational lifting and being overweight may be important risk factors for retinal detachment among people with myopiaò, and concludes that ñthe role of these risk factors in the aetiology of retinal detachment deserves to be explored in more general populationsò.

The aim of the present study is to test the following hypotheses in a general working population:

1. The rate of rhegmatogenous retinal detachment is higher among workers in occupations strongly associated with heavy lifting than it is among blue-collar workers in occupations in which heavy lifting is less likely to occur.

2. The rate of rhegmatogenous retinal detachment is higher among workers in occupations strongly associated with heavy lifting than it is among white-collar workers in occupations in which heavy lifting is unlikely to occur.

The above hypotheses tests are operationalisations designed to shed light on our underlying hypothesis which states that ñoccupational heavy lifting in general working populations is positively associated with retinal detachment and plays an important role in its aetiologyò.

The theoretical reason behind the hypothesis is that the exertion of great physical force while holding ones breath will cause the body to perform the Valsalva maneuver involuntarily. The frequent and prolonged variation in intraocular pressure caused by the Valsalva manoeuver may increase the risk of retinal detachment, because of some possible mechanisms as well as vitreal traction, raised pressure in the choroid, and possibly even recurrent Valsalva hemorrhagic retinopathy. It is heavy lifting that we think is most likely to increase risk, not prolonged or frequent lifting of smaller weights. After an experimental study Pivovarov et al. (1977) indicated in 15 kg the weight that, lifted, increased the intraocular pressure.

Project organisation

The project is a collaboration between Professor David Coggon, University of Southampton, Professor Stefano Mattioli, University of Bologna and Dr. Elsa Bach, the Danish National Research Centre for the Working Environment (NRCWE). Coggon and Mattioli initiated the project and will provide the medical expertise necessary for its accomplishment. The statistical analyses of the project will be performed at NRCWE.

All services provided by NRCWE will be delivered in accordance with recognised rules of good scientific and statistical practice. With regard to hypothesis testing, such rules dictate that both the hypothesis and the statistical model(s) are completely defined before we look at any relation between the concerned exposure and response variables in our data material. It also dictates that any post hoc tests will be labelled as such when results are reported. A detailed study protocol is to be written and agreed upon by all parties before any statistical hypothesis test is performed.

Material

The study will use the Danish Occupational Hospitalisation Register (OHR), a database obtained through a record-linkage between three national registersð the central person register [Pedersen, 2011], the hospital patient register [Lynge et al., 2011], and the employment classification module. Currently, the OHR includes every person who has been economically active and an inhabitant of Denmark sometime after 1980. The central person register contains information on gender, addresses and dates of birth, death and migrations for every person who is or has been an inhabitant of Denmark sometime between 1968 and present time. A personõs occupation and industry are, since 1975, registered annually in the employment classification module. Since 1994, the occupations are coded according to DISCO-88 [Statistics Denmark, 1996], which is a national version of ISCO-88 (the International Standard Classification of Occupations). The national hospital register has existed since 1977 and contains data from all public hospitals in Denmark (more than 99% of all admissions). From 1977 to 1994, the register only included inpatients but from 1995 it also covers outpatients and emergency ward visits. The diagnoses are coded according to ICD-10, since 1994.

Occupational categories

The occupations were categorised according to expert opinions. Dr. Holtermann, National Research Centre for the Working Environment (NRCWE) selected the occupations to be associated with heavy lifting while

Professor Coggon, University of Southampton, selected the occupations in which heavy lifting is unlikely to occur. The opinion of Holtermann was seconded by Professor Karen Søgaard, University of Southern Denmark. The occupational categories are given, in terms of DISCO-88 codes, in table 1.

Table 1. Occupational categories according to DISCO-88

Occupational category	DISCO-88
Holtermannôs group (Occupations which are strongly associated with heavy lifting)	712. Building frame and related trades workers 921. Agricultural, forestry and fishery labourers 931. Construction labourers 933. Transport and storage labourers
Coggon's blue-collar workers (Occupations in which heavy lifting is unlikely to occur)	731 Precision workers in metal and related materials 733. Handicraft workers in wood, textile, leather and related material 734. Printing and related trades workers 741. Food processing and related trades workers 743. Textile, garment and related trades workers 744. Pelt, leather and shoemaking trades workers 815. Chemical-processing-plant operators 816. Power-production and related plant operators 817. Automated-assembly-line and industrial-robot operators 822. Chemical-products machine operators 825. Printing-, binding-and paper-products machine operators 826. Textile-, fur-and leather-products machine operators 827. Food and related products machine operators 828. Assemblers 829. Other machine operators and assemblers 831. Locomotive engine drivers and related workers 912. Shoe cleaning and other street services elementary occupations 913. Domestic and related helpers, cleaners and launderers 914. Building caretakers, window and related cleaners
Other blue-collar workers	All workers with a first digit DISCO-code equal to 6 (agricultural trades workers), 7 (craft and related trades workers), 8 (plant and machine operators and assemblers) or 9 (elementary occupations). Except those that belong to either Holtermannôs group or Coggon's blue-collar workers.
Coggon's white-collar workers (Occupations in which heavy lifting is unlikely to occur)	All workers with a first digit DISCO-code equal to 1 (legislators, senior officials and managers), 2 (professionals), 3 (technicians and associate professionals) or 4 (clerks). Except those that belong to the following occupations: 223. Nursing and midwifery professionals 323. Nursing and midwifery associate professionals 347. Artistic, entertainment and sports associate professionals

Validation of expert opinions

Data from the Danish work environment cohort survey (DWECS) in the calendar year 2000 were used to confirm that the occurrence of heavy lifting among male workers who belong to Holtermannôs group is significantly higher than it is among workers who belong to the other occupational categories. Responses to the following questions were regarded:

- How much of your time at work do you carry or lift objects? (*Almost all the time; Approximately 3/4 of the time; Approximately 1/2 of the time; Approximately 1/4 of the time; Rarely/very little; Never*)

- How much does what you carry or lift typically weigh? (*Less than 3 kg; 3-10 kg; 11-29 kg; 30-49 kg: 50 kg or more*)

Percentages of lifters are given, by occupational category, in table 2 ï 3. The proportion who reported that they carry or lift objects approximately ¼ of the time or more was statistically significantly higher among males in Holtermannôs group than it was among Coggon's blue-collar workers (P<0.0001), other blue-collar workers (P<0.0001) and Coggon's white-collar workers (P<0.0001). The same holds for the ones who reported that they carry or lift objects approximately ¼ of the time or more and that the objects typically weigh 30 kg or more (P = 0.015; P = 0.007; P < 0.0001).

Table 2. Percentage of male workers who carry or lift objects approximately 1/4 of the time or more according to DWECS 2000

Occupational group	N	Lifters	Percent	Low_95	High_95
Holtermannôs blue-collar workers	260	206	79.2	74.5	84.3
Coggon's blue-collar workers	185	103	55.7	49.0	63.3
Other blue-collar workers	889	410	46.1	43.0	49.5
Coggon's white-collar workers	1592	246	15.5	13.8	17.3

Table 3. Percentage of male workers who report that they carry or lift objects approximately 1/4 of the time or more and that the objects typically weigh 30 kg or more (DWECS 2000).

Occupational group	N	Heavy Lifters	Percent	Low_95	High_95
Holtermannôs blue-collar workers	260	43	16.5	12.6	21.7
Coggon's blue-collar workers	185	17	9.2	5.8	14.5
Other blue-collar workers	889	97	10.9	9.0	13.2
Coggon's white-collar workers	1592	40	2.5	1.9	3.4

Study design

A dynamic cohort (open for both entry and departure) of all 20-59-year-old men in Denmark will be followed in the Danish Occupational Hospitalisation Register (OHR), from 1 January 1995 to 31 December 2010, for hospital contacts with retinal detachment with retinal break (ICD-10 = H33.0) as principal diagnosis. Each person is followed until any of the following events occur: he reaches the clinical endpoint of the study, he is treated at a hospital with ôinjury of eye and orbitö (ICD-10 = S05) as principal diagnosis, he emigrates, he dies, he becomes 60 years old, the study period ends. Time-dependent dummy variables (which are updated 1 January each calendar year) are used to indicate whether or not a person belongs to a specific occupational category. While adjusting for calendar year (4-year intervals) and age (10-year age groups), we will use Poisson regression to estimate the following rate ratios (RR):

RR1. Holtermannös blue-collar workers vs. Coggonös blue-collar workers

RR2. Holtermannös blue-collar workers vs. all other blue-collar workers

RR3. Holtermannös blue-collar workers vs. Coggonös white-collar workers

Each of the rate ratios will be presented with 95% confidence intervals. Proc genmod in SAS version 9.3 will be used to implement the analysis.

Hypothesis testing criteria

The first hypothesis is confirmed (regarded as statistically significant) if both RR1 and RR2 are greater than one, and the lower boundary of at least one of the two 95% confidence intervals exceeds one.

The second hypothesis is confirmed if the lower boundary of the 95% confidence interval of RR3 exceeds one.

Our overall hypothesis is that the results of the study will support the underlying hypothesis of the study. This hypothesis is confirmed (i.e. we will conclude that the results of the study supports the underlying hypothesis) if i) the lower boundary of at least one of the three estimated 95% confidence intervals exceeds one, and ii) both of the estimated rate ratios (the point estimates) of the first hypothesis are greater than one.

Power calculations

We estimate that the expected numbers of non-injury related cases of rhegmatogenous retinal detachment among 20 ï 59 year-old men in the time period 1995 ï 2010 are approximately: 250 in Holtermannös group, 180 among Coggonös blue-collar workers, 850 among other blue-collar workers, and 1500 among Coggonös white-collar workers. The estimates are based on i) the incidence in the year 2000, among all men aged 20 ï 59 years in Denmark, ii) the number of workers by occupational category in that year, and iii) the assumption that approximately 10% of the cases of rhegmatogenous retinal detachment are due to an ôinjury of eye and orbitö.

Approximate statistical powers for the first, second and overall hypothesis are given in table 4, as a function of the rate ratio between workers in Holtermannös group and workers in the comparison group(s). The probability for type I error of the various hypotheses tests are given in the first row of the table (RR = 1.00). The probability that we, due to chance alone, conclude that the data supports the underlying hypothesis is approximately equal to 0.05.

Table 4. Approximate statistical powers for the first, second and overall hypothesis are given in table 4, as a function of the rate ratio between workers in Holtermannǿs group and workers in the comparison group(s).

RR	First hypothesis	Second hypothesis	Overall hypothesis
1.00	0.0412	0.0250	0.0523
1.05	0.1389	0.1128	0.1779
1.10	0.3312	0.3096	0.4071
1.15	0.5792	0.5744	0.6678
1.20	0.7941	0.8007	0.8600
1.25	0.9223	0.9299	0.9557
1.30	0.9774	0.9813	0.9892
1.35	0.9948	0.9962	0.9980
1.40	0.9991	0.9994	0.9997
1.45	0.9999	0.9999	1.0000
1.50	1.0000	1.0000	1.0000

The powers were calculated by means of Monte Carlo simulation. The following SAS program was used:

```
options mprint;
%macro simul1; %do True_rr = 100 %to 150 %by 5;

data test;

   True_rr = &True_rr/100;

   Total = 250 + 180 + 850 + 1500;

   c = Total/(Total + 250*(True_rr-1));

   do i = 1 to 10000000;

     x0 = rand('poisson',250*True_rr*c);
     x1 = rand('poisson',180*c);
     x2 = x1 + rand('poisson',850*c);
     x3 = rand('poisson',1500*c);

     rr1 = x0/x1*180/250; rr2 = x0/x2*(180 + 850)/250; rr3 = x0/x3*1500/250;

     low1 = exp(log(rr1) - 1.96*sqrt(1/x0 + 1/x1));
     low2 = exp(log(rr2) - 1.96*sqrt(1/x0 + 1/x2));
     low3 = exp(log(rr3) - 1.96*sqrt(1/x0 + 1/x3));

     hypothesis1 = 0;
     if (low1 > 1 and rr2 > 1) or (low2 > 1 and rr1 > 1) then hypothesis1 = 1;
     hypothesis2 = 0;
     if low3 > 1 then hypothesis2 = 1;
     overall_hypothesis = 0;
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      if hypothesis1 = 1 or (low3 > 1 and rr1 > 1 and rr2 >1) then
        overall_hypothesis = 1;

      output;
    end;
run;

proc means; var True_rr hypothesis1 hypothesis2 overall_hypothesis; run;

%end; %mend simul1;

%simul1
```

The role of cataract surgery as a potential confounder

It has been shown that cataract surgery increases the risk of rhegmatogenous RD; the rate ratio has been estimated to 4.23 [Bjerrum et al., 2013]. Since a substantial share of this type of surgical procedure is performed by private practitioners who do not report to the patient registry [Kat-Base, 2005], we cannot control this factor in the present study. Since we cannot control for it, we need to evaluate its potential to distort the results of our study. In particular, we want to know the population attributable fraction (PAR) for cataract surgery on the risk of RD among 20 - 59 year old men in Denmark; a rough estimate will suffice.

The population attributable fraction (see Laaksonen, 2010) is given by the equation

$$PAR = \frac{p(RR-1)}{1+p(RR-1)}$$

where p is the proportion of people who have undergone cataract surgery and RR is the rate ratio between operated and non-operated people.

In order to calculate the population attributable fraction, we need to estimate p.

Assumptions

- Approximately 46000 cataract operations are performed per year in Denmark (see Kat-Base, 2005) and 40% of the operations concern the second eye on previously treated people (see Bjerrum et al., 2013). This implies a total number of 27600 new cases of cataract operated persons per year.
- The number of operations among people younger than 40 years is negligible (see NOMESCO, 2006).
- The age and gender distribution among the people who receives cataract surgery in Denmark is given by Bjerrum et al. (2013); 1.1% of the operations concern 40 ï 49 year old men, while 3.4% concern 50 ï 59 year old men.

If we relate the above to the Danish population in 2004, we get 79 and 244 new cases per 100 000 person years at risk among the 40 ï 49 and 50 ï 59 year old men respectively. If we, moreover, assume that the rates of cataract surgery within the age categories are constant (this simplification will give us a liberal estimate) and that the population has a uniform age distribution, then all of the above assumptions and estimates imply that the prevalence of cataract operated people among the 40 ï 59 year old men in Denmark is approximately equal to 1.2%.

In mathematical terms, the prevalence among men in the age interval [k, k + 1) years is given by the equation

$$p_k = 1 - \left(\prod_{i=40}^{k} (1 - q_{i-1}) + \prod_{i=40}^{k} (1 - q_i) \right) / 2$$

where q_i = 0 for i < 40, 79 / 100 000 for 40 Ò i Ò49, and 244 / 100 000 for 50 Ò i Ò59. The overall prevalence in the age interval [40, 60) is given by the equation

$$p = \frac{1}{20} \sum_{k=40}^{59} p_k$$

The above prevalence estimate and rate ratio imply that the population attributable fraction for cataract surgery on the risk of RD among 40 - 59 year old men in Denmark equals 3.7%. The literature suggests that it is negligible for people who are less than 40 years old [Kat-Base, 2005; NOMESCO, 2006].

Discussion

With this study protocol, we define all hypotheses, inclusion criteria, statistical models and test criteria completely before the statistical analyses are commenced. By doing so, we have eliminated hindsight bias. Other strengths of the present study are quite well summarised by the following quotation from a protocol of a previous study, which used the same data material: ñOur follow-up is done prospectively through registers and does not require that the participants should fill in a questionnaire. Hence we do not have any problems with recall bias or non-response bias. Since informed consent from the participants is not required for register studies of the present type, the study is free from volunteer bias. It is also free from sampling bias since all people in the target population are included. Another advantage of the study is that referral bias is minimal; the diagnoses under study are of a kind that requires hospital treatment. The study is further strengthened by its size.ò [Hannerz et al., 2010]

The weakness of the study is its lack of individual based data, not only on occupational heavy lifting but also on some quite important non-lifting related risk factors for retinal detachment (RD), such as diabetes [Kollias et al., 2010], injury [Mitry et al., 2011] and myopia [The Eye Disease Case-Control Study Group, 1993]. The last mentioned reference suggests that almost 55% of nontraumatic detachments in eyes without previous surgery are attributable to myopia.

The prevalence of myopia increases with educational level and tends to be much higher among white-collar workers than it is among blue-collar workers [e.g. Sperduto et al., 1983; Saw et al., 1996]. The relationship between education and myopia holds not only for people with mild myopia but for myopes of all degrees [Teasdale et al, 1988, Rahi et al., 2011, Bar Dayan et al., 2005; Chew et al., 1988; Au Eong et al., 1993]. Moreover, several studies indicate that the relationship is stronger for severe myopia than it is for mild myopia [Bar Dayan et al., 2005; Chew et al., 1988; Au Eong et al., 1993]. On the other hand, in the EPIC-Norfolk Eye Study, there were no major differences in refractive error, between manual and non manual workers [Foster et al., 2010].

Another potential confounder, which we do not control, is leisure time heavy lifting. In modern societies, heavy lifting at work is more or less prohibited by work environmental regulations. Leisure time lifting, on the other hand, is a completely unregulated activity.

In the present study, the possible confounding from diabetes is handled by the decision to only include rhegmatogenous RD in the case definition. Types of RD known to be associated with diabetes are thereby excluded from the analysis. Injury related confounding will be mitigated by our strategy to exclude workers from further follow-up if and when they, according to the hospital patient register, incur an injury to the eye or orbit. The possible confounding from cataract surgery will be minimal, since we only deal with people who are less than 60 years.

To mitigate myopia related confounding, we decided to only include blue-collar workers in our primary comparison group. The drawback of this decision is that the comparison group also, to some degree, will contain elements of heavy lifting.

Our secondary hypothesis test (workers in Holtermannӧs group vs. Coggonӧs white-collar workers) might be highly influenced by differences in myopia prevalence. This needs to be taken into account when we evaluate the results.

Ethics approval

The study will comply with The Act on Processing of Personal Data (Act No. 429 of 31 May 2000), which implements the European Union Directive 95/46/EC on the protection of individuals. The data usage is approved by the Danish Data Protection Agency, journal number: 2001-54-0180. According to Danish law, questionnaire and register based studies do not need approval by ethical and scientific committees, nor informed consent.

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