COMMISSIONED REPORT

The risk of ischemic heart disease and stroke according to a range of work-related psychosocial exposures: a systematic review with meta-analyses.

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(1) Department of Occupational and Environmental Medicine, Bispebjerg and Frederiksberg Hospital, Copenhagen
(2) Department of Epidemiology, Columbia University, New York
(3) Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, and Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden
(4) Psychosocial Safety Climate Global Observatory, University of South Australia, Adelaide

Content

FOREWORD

Following an open international call for a 'Review of the correlation between exposure to mental stress in the working environment and the development of cardiovascular disease' issued by the Danish Work Environment Fund with a deadline for applications September 2th 2024, this report was drafted by a local team of researchers at the Department of Occupational and Environmental Medicine at Bispebjerg-Frederiksberg University Hospital, Copenhagen, in collaboration with international renowned scientists within epidemiology, psychosocial workplace exposures and cardiology. Two independent peer reviewers suggested by the authors, and authorised by the Work Environment Fund, reviewed the preliminary draft. This final report includes author responses to the external review comments.

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The report was formatted according to the requests from the Danish Working Environment Fund. The evidence for causal associations between specified workplace exposures and cardiovascular disease outcomes was graded into categories originally suggested by The Danish Society of Occupational Medicine based on general principles for causal inference in epidemiology, which are also applied by for example the GRADE system. A list of abbreviations in text, tables and figures is provided in Annex I.

The authors, September 2025,

Jens Peter Bonde, professor emeritus, Dr Med, Department of Occupational and Environmental Medicine, Bispebjerg and Frederiksberg University Hospital, Copenhagen

Stinna Skaaby, consultant physician, PhD, Department of Occupational and Environmental Medicine, Bispebjerg and Frederiksberg University Hospital, Copenhagen

Esben Meulengracht Flachs, statistician, PhD, Department of Occupational and Environmental Medicine, Bispebjerg and Frederiksberg University Hospital, Copenhagen

Ingrid Alethe Sivesind Mehlum, professor, PhD, Department of Occupational and Environmental Medicine, Bispebjerg and Frederiksberg University Hospital, Copenhagen

Sigurd Mikkelsen, former chief physician, Dr Med, Department of Occupational and Environmental Medicine, Bispebjerg and Frederiksberg University Hospital, Copenhagen

Katharine Keyes, professor, PhD, Department of Epidemiology, Columbia University, New York, USA

Annika Rosengren, cardiologist, professor of medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Maureen Dollard, research director, Laureate professor, Psychosocial Safety Climate Global Observatory, University of South Australia, Adelaide, Australia

DANSK SAMMENFATNING

INTRODUKTION

Iskæmisk hjertesygdom (åreforkalkning i hjertets kranspulsårer) og stroke (slagtilfælde som følge af blodprop eller blødning i hjernen) tegner sig for hovedparten af de kardiovaskulære sygdomme. Til trods for et dramatisk fald i særligt dødeligheden af iskæmisk hjertesygdom gennem de seneste 40 år er nedgangen nu aftagende og kardiovaskulære sygdomme bidrager fortsat afgørende til både sygelighed og dødelighed.

Der er forsket i arbejdsrelaterede psykosociale stressorer og hjertekarsygdom i mere end 50 år og de seneste 10-15 år er der publiceret et stort antal systematiske *reviews (*senest i 2021) *og to meta-reviews (review af reviews)* om sammenhæng mellem arbejdsrelaterede psykosociale stressorer og fortrinsvis hjertesygdom og stroke. Det er imidlertid omdiskuteret om rapporterede sammenhænge kan betragtes som kausale. Problemerne knytter sig blandt andet til mangelfuld dokumentation og præcisering af eksponeringens karakter, som i langt de fleste undersøgelser er baseret på selvrapporterede data. For eksempel er det indtil videre uklart om associationen med *job strain* skyldes kombinationen af høje krav og lav kontrol – som det ofte antages – eller alene lav kontrol, som er særligt sårbar for social confounding. En række andre metodologiske problemer kan bevirke bias (skævvridning) i retning af for svage eller for stærke sammenhænge.

FORMÅL

Undersøgelsens formål er at vurdere den videnskabelige evidens for årsagsmæssig sammenhæng mellem arbejdsrelaterede psykosociale påvirkninger og udvikling af hjertekarsygdom på basis af en opdateret systematisk oversigt og kritisk gennemgang af den internationale epidemiologiske litteratur på området. Det overordnede formål blev afgrænset i følgende delformål:

(1) At sammenfatte og vurdere den epidemiologiske og medicinske evidens for risikoen for iskæmisk hjertesygdom (herunder akut myokardie infarkt, angina pectoris og akut koronarsyndrom) samt stroke (slagtilfælde, apoplexia cerebri, iskæmisk og hæmoragisk stroke) som følge af henholdsvis job strain, indsats belønnings-ubalance, job usikkerhed, lang arbejdstid, vold, trusler og mobning, organisatoriske forandringer og andre psykosociale arbejdsmiljø-påvirkninger i det omfang der foreligger relevante studier.

(2) I videst muligt omfang at kvantificere sygdomsrisikoen i forhold til eksponeringens intensitet og varighed (dosis-respons), at vurdere konsistens på tværs af studier, herunder fokus på studier med alternative designs og mål for eksponering (triangulering) samt at afklare i hvilket omfang de enkelte dimensioner i *job strain* modellen (effekt af henholdsvis krav, kontrol og social støtte) og *effort-reward inbalance* modellen (indsats, belønning og commitment) ligger til grund for kombinerede effekter.

(3) At vurdere eksperimentelle og epidemiologiske data om sammenhængen mellem psykosociale eksponeringer og etablerede risikofaktorer for iskæmisk hjertesygdom (hypertension, livsstil, biomarkører) i den sammenlede vurdering af evidensen for kausalitet.

Projektet er efter opdrag fra Arbejdsmiljøforskningsfonden udført af en international forskergruppe med ekspertise indenfor arbejdsmedicin, epidemiologi, kardiologi, biostatistik og psykosocialt arbejdsmiljø i tidsrummet 1.1-31.9 2025.

FREMGANGSMÅDE

Litteratursøgning og dataekstraktion

Der blev foretaget en systematisk litteratursøgning i PubMed (fra 1966 og frem) og Embase (fra 1947 of frem) til og med den 15-16. november 2024 med henblik på at identificere originale fagfællebedømte epidemiologiske undersøgelser omhandlende sammenhængen mellem arbejdsrelaterede psykosociale påvirkninger og iskæmisk hjertesygdom og/eller stroke.

Ved den initiale brede litteratursøgning fandtes 3.396 publikationer, som blev uafhængigt screenet af to forfattere med henblik på at afklare om de på forhånd fastsatte inklusionskriterier var opfyldte. Dette skete ved læsning af abstracts i langt de fleste tilfælde, men 167 artikler blev læst i deres helhed. I undersøgelsen indgik kun kohorte- og nestede case-control-studier med kvantitative mål for sammenhæng mellem psykosocial arbejdseksponering og iskæmisk hjertesygdom (inklusive angina pectoris (hjertekrampe), men ikke hypertension (forhøjet blodtryk) eller stroke diagnosticeret ved medicinske kriterier, og med risiko-estimater, der som minimum tog højde for køn, alder og mindst ét mål for socioøkonomisk status. Studier, der byggede på personens egen genkaldelse af eksponeringer efter sygdommens optræden, eller som anvendte helt eller delvist selvrapporterede sygdomsudfald – herunder selvrapporterede lægediagnoser – blev udelukket.

Yderligere fire relevante studier blev identificeret via referencelister, hvilket bragte det samlede antal inkluderede studier op på 59. Tilsammen bidrog disse studier med 315 relevante risikoestimater. Resultatet af litteratursøgning og udvælgelse af artikler blev valideret ved at krydstjekke mod de originale artikler, der var inkluderet i tidligere systematiske reviews.

Alle inkluderede artikler blev gennemgået med henblik på systematisk udtræk af den relevante information på en ensartet måde, herunder data vedrørende demografiske karakteristika, studiedesign, studiepopulation, antal eksponerede og ueksponerede, type eksponering, mål for eksponering, udfaldsdefinition, strata (køn, socialgruppe), eksponeringskategorier, rå og justerede risikoestimater med 95% sikkerhedsgrænser samt hvilke potentielle confoundere der indgik i analyserne.

Sammenfatning og vurdering af kausal evidens

Vi sammenfattede risiko-estimater inden for og på tværs af studier i grafiske oversigter (*forest plots*) stratificeret efter eksponeringstype og sygdom (iskæmisk hjertesygdom, stroke) samt ved beregning af gennemsnitlige risikoestimater vægtet på basis af studie størrelse således at større studier indgik med større vægt (random-effects meta-analyse). Hvis et studie rapporterede flere estimater for en given sammenhæng mellem eksponering og sygdom, f.eks for mænd og kvinder eller *white- and blue-collar workers* beregnede vi et enkelt gennemsnitligt risiko-estimat. Når flere eksponeringsniveauer blev rapporteret, blev det højeste eksponeringsniveau anvendt i de samlede estimater. For hver eksponeringstype vurderedes risikoen for henholdsvis hjerte-kar-sygdom, kombineret iskæmisk hjertesygdom og slagtilfælde, samt risici for mere specifikke sygdomsudfald, f.eks. myokardie infarkt eller hjerneblødning. I supplerende analyser undersøgte vi, om sammenhænge mellem eksponering og udfald blev påvirket af faktorer som køn, socioøkonomisk position, udfaldsspecificitet, uafhængig eksponeringsvurdering, deltagelsesgrad, kalenderperiode, opfølgningslængde samt inklusion af potentielle effektmodifikatorer i de statistiske modeller (fx medicinske og adfærdsmæssige risikofaktorer for iskæmisk hjertesygdom). I analyserne af risiko i forhold til ugentlig arbejdstid blev de oprindelige kategorier fra studierne omklassificeret til fire grupper (<35 timer/uge, 35–40 timer/uge, 41–55 timer/uge, >55 timer/uge).

Vurderingen af kausal evidens var baseret på konsistens mellem forskellige populationer og studiedesigns, associationens styrke, eksponerings-respons, specificitet, bias og confounding samt biologisk plausibilitet, mens meta-analytiske risiko-estimater alene tjente til at skabe et overblik over retning og styrke af risiko-estimaterne. Den endelige vægtning af vurderingen sammenfattedes på basis af Arbejdsmiljøforsknings-fondens evidenskriterier.

RESULTATER

Datagrundlaget omfattede 57 opfølgningsstudier og to case-control-studier, hvoraf de fleste omhandlede risikoen for iskæmisk hjertesygdom. Hovedparten af studierne blev gennemført i Europa og inkluderede både stikprøver fra den generelle befolkning og arbejdspladsbaserede populationer. Oplysninger om eksponering blev i de fleste opfølgningsstudier indhentet via selvrapportering ved baseline, men ni studier anvendte job-eksponeringsmatricer eller andre uafhængige mål for psykosociale arbejdsmiljøeksponeringer.

Sygdommen blev oftest defineret på basis af hospitalsudskrivningsdiagnoser eller dødsattester, selvom en mindre del af studierne identificerede nye sygdomstilfælde ved kliniske undersøgelser i opfølgningsperioden.

Omtrent en tredjedel af opfølgningsstudierne inkluderede deltagere før 1990, og i en tredjedel af studierne var deltagelsesraten under 75 %. Opfølgningsperioden varierede fra 1 til 30 år med en median på 9,9 år. Kun en mindre del af studierne undersøgte meget specifikke udfald som blodprop i hjertet (myokardieinfarkt) eller skelnede mellem iskæmisk og hæmoragisk stroke.

Job strain og DCS-modellen

Ifølge demand-control-support (DCS) modellen for arbejdsstress øger *job strain* – defineret som kombinationen af høje arbejdskrav (arbejdsmængde og tidspres) og lav kontrol (begrænset beslutningskompetence og lav indflydelse på arbejdets udførelse) – risikoen for negative helbredseffekter. Derudover antages det, at høj grad af social støtte på arbejdspladsen kan dæmpe de negative effekter af *job strain*. Kombinationen af høje krav, lav kontrol og lav støtte betegnes *iso-strain*, hvor "iso" refererer til isolation. Modellen forudsætter, at effekten af job strain opstår gennem samspillet mellem krav og kontrol, uafhængigt af deres individuelle effekter, og i sin fulde form også gennem samspil med social støtte.

Vi identificerede i alt 25 opfølgningsstudier og ét case-control-studie med 49 estimater af sammenhængen mellem job strain og hjerte-kar-sygdom. De fleste studier var gennemført i Europa og omfattede både befolkningsundersøgelser og arbejdspladsbaserede populationer. Størrelsen på deltagergrupperne varierede fra cirka 1.500 til flere millioner personer. Eksponeringsdata blev hovedsageligt indsamlet via spørgeskema med angivelse af grad af job krav, kontrol (indflydelse og udviklingsmuligheder) og eventuelt social støtte på en skala.

Det primære udfald var iskæmisk hjertesygdom, mens kun få studier undersøgte slagtilfælde. Job strain blev typisk vurderet ved at kombinere høje krav og lav kontrol, oftest dikotomiseret ved medianen af skalaværdier for krav og kontrol – enten mod alle andre grupper eller mod gruppen med lave krav og høj kontrol.

Samlede analyser viste sammenhænge mellem job strain og hjerte-kar-sygdom efter fuld justering. De gennemsnitlige variansvægtede risiko-estimater (Hazard Ratio, HR) var:

- **1,13** (95 % CI 1,06–1,21; 26 studier med 49 risikoestimater) for hjerte-kar-sygdom samlet,
- **1,14** (95 % CI 1,06–1,23; 21 studier med 32 risikoestimater) for iskæmisk hjertesygdom, og
- **1,19** (95 % CI 1,03–1,37; 7 studier med 13 risikoestimater) for stroke.

Der var indikationer på højere risiko i studier uden for Norden, blandt ufaglærte arbejdere, og i studier baseret på selvrapporterede eksponeringer. Sammenhængene var stærkere i analyser, der ikke justerede for adfærdsmæssige og medicinske risikofaktorer. Til gengæld rapporterede studier med job-eksponeringsmatricer svagere sammenhænge. Køn havde ikke nogen klar betydning. To studier undersøgte tidsvarierende eksponering og fandt sammenhænge med både aktuelle og akkumulerede niveauer af job strain.

Iso-strain, kombinationen af lav social støtte og job strain, var forbundet med hjerte-kar-sygdom samlet set i meta-analysen (HR 1,21; 95 % CI 1,06–1,38; 4 studier med 9 risikoestimater). Resultaterne i de enkelte studier var dog modstridende. Høje krav, lav kontrol og lav støtte hver for sig var alle forbundet med hjerte-kar-sygdom (meta-analytiske HR: høje krav 1,02; 95 % CI 0,96–1,09; 19 studier med 35 risikoestimater; lav kontrol HR 1,03; 95 % CI 1,03–1,12; 24 studier med 47 risikoestimater; lav social støtte HR 1,10; 95 % CI 1,00–1,21; 9 studier med 18 risikoestimater). Der var ingen tegn på dosis-respons-sammenhænge for nogen af disse eksponeringer.

Resultaterne er i overensstemmelse med 11 tidligere systematiske reviews, herunder to oversigtsartikler.

Af betydning for vurdering af evidens for kausalitet kunne konstateres betydeligt varierende risikoestimater mellem studier, beskedne associations styrker og manglende dokumentation af eksponerings-respons sammenhænge. Derudover er bias vanskelig at vurdere, da nogle typer bias forventes at svække risikoestimater, mens andre typer af bias forventes ar resultere i forstærkede risikoestimater, En yderligere svaghed er manglende bekræftelse af fundene gennem uafhængige eksponeringsmålinger og manglende justering for DCS-modellens grundkomponenter i de fleste studier. Endelig synes publikationsbias at være et særskilt problem i relation til job strain.

Anstrengelses-belønnings-ubalance modellen

Ifølge anstrengelses-belønnings-ubalance (Effort-Reward Imbalance, ERI) modellen fører høj arbejdsindsats kombineret med lav belønning til negative helbredseffekter, som forstærkes, hvis personen er *overcommitted* i sit arbejde. Igen forstås effekterne som resultatet af samspillet mellem indsats og belønning, uafhængigt af de enkelte komponenters individuelle virkninger.

Tre opfølgningsstudier med seks risikoestimater undersøgte sammenhængen mellem ERI og risikoen for iskæmisk hjertesygdom. Disse omfattede Whitehall-studiet blandt britiske embedsmænd, et studie af elleve europæiske kohorter (IPD-Work konsortiet) samt et studie af canadiske kontoransatte. Et yderligere studie undersøgte udelukkende effekterne af *overcommitment*. Forskellige selvrapporterede mål for ERI blev anvendt, hovedsageligt baseret på ratioen mellem skalaværdier for indsats og belønning dikotomiseret som >1,0 versus ≤1,0. Ingen studier undersøgte risikoen for stroke i relation til ERI.

Alle studier fandt konsistent, at ERI var forbundet med iskæmisk hjertesygdom (gennemsnitlig meta-analytisk HR 1,18; 95 % CI 1,03–1,35; 3 studier med 4 risikoestimater), men uden eksponerings-respons-mønstre. Ét studie rapporterede en sammenhæng kun blandt mænd. Separate analyser af høj indsats og lav belønning viste også sammenhænge (gennemsnitlig meta-analytisk HR for høj indsats 1,07; 95 % CI 0,85–1,36; HR for lav belønning 1,11; 95 % CI 0,92–1,34).

Ingen studier vurderede interaktive effekter mellem indsats og belønning i relation til iskæmisk hjertesygdom. Ét studie fandt ingen evidens for, at *overcommitment* forstærkede effekten af ERI. IPD-Work konsortiet rapporterede, at sammenhængen mellem ERI og iskæmisk hjertesygdom var uafhængig af *job strain*. Ingen studier undersøgte ERI i forhold til stroke.

En tidligere systematisk oversigt konkluderede, at evidensen for ERI og iskæmisk hjertesygdom er begrænset, men nyere studier – som ikke var med i den oversigt – støtter en sammenhæng.

Af betydning for vurdering af evidens for kausalitet anføres grove mål for eksponering, som kun blev vurderet ved baseline, manglende data om eksponerings-respons, beskedne associationsstyrker, som kan skyldes residual confounding, samt manglende justering for indsats og belønning i to af de tre studier.

Jobusikkerhed

Jobusikkerhed defineret som frygten for at miste sit job, usikkerhed om fortsat ansættelse eller ansættelse i en virksomhed under nedskæringer er en mulig risikofaktor for hjerte-kar-sygdom. Foreslåede mekanismer omfatter søvnforstyrrelser, usund adfærd, psykologisk distress med aktivering af autonome eller endokrine stressreaktioner.

Seks prospektive studier undersøgte oplevet jobusikkerhed i relation til iskæmisk hjertesygdom, mens to studier vurderede hjerte-kar-sygdom efter nedskæringer eller organisatoriske ændringer. Den vægtede gennemsnitlige risiko for iskæmisk hjertesygdom var HR 1,16 (95 % CI 1,05–1,28) i de seks studier om oplevet jobusikkerhed. Det største studie gennemført af IPD-Work konsortiet rapporterede en fuldt justeret HR for myokardieinfarkt (blodprop i hjertet) på 1,05 (95 % CI 0,90–1,24). Tidligere kohortestudier rapporterede højere risikoestimater (HR 1,19–2,50), men kun få resultater var statistisk signifikante. Kun ét studie undersøgte stroke og fandt ingen sammenhæng med jobusikkerhed.

Et finsk registerstudie fandt ingen øget risiko for dødelighed af iskæmisk hjertesygdom efter *downsizing* (reduktion af arbejdsstyrken med afskedigelser), mens et dansk studie antydede en højere risiko for hjerte-kar-sygdom efter organisatorisk omstrukturering. Et andet finsk registerstudie rapporterede en fordoblet risiko for kardiovaskulær dødelighed i relation til *downsizing*, men dette studie opfyldte ikke inklusionskriterierne, fordi sygdommen ikke var afgrænset til iskæmisk hjertesygdom eller stroke men omfattede alle typer af hjerte-kar-sygdomme.

Tidligere systematiske reviews har konkluderet, at der er begrænset til moderat evidens for en sammenhæng mellem jobusikkerhed og iskæmisk hjertesygdom. Socioøkonomiske faktorer og livsstilsforhold kan bidrage til de observerede sammenhænge.

Af betydning for vurdering af evidens for kausalitet anføres grove og diverse mål for eksponering, manglende eksponerings-respons-analyser, mulig residual confounding samt inkonsistente resultater i studier af *downsizing.*

Lang arbejdstid

Lang ugentlige arbejdstid er foreslået at kunne øge risikoen for hjerte-kar-sygdom gennem flere mulige mekanismer: udmattelse, manglende restitution, nedsat søvn, mindre fysisk aktivitet i fritiden, social isolation, konkurrencepræget adfærd og usunde vaner som dårlig kost.

Ni epidemiologiske studier med 54 risikoestimater undersøgte sammenhængen mellem lange arbejdsuger og hjerte-kar-sygdom. Eksponering var selvrapporteret i alle studier bortset fra ét case-control-studie, som delvist anvendte nedskrevne lønoplysninger til støtte for fastlæggelse af den ugentlige arbejdstid.

Sammenlignet med standardarbejdstid (35–40 timer/uge) fandtes ingen øget risiko ved 41–55 timer/uge (gennemsnitlig vægtet HR 1,02; 95 % CI 0,93–1,12). For >55 timer/uge sås en lille, ikke-signifikant forhøjelse af den samlede risiko for hjerte-kar-sygdom (gennemsnitlig vægtet HR 1,09; 95 % CI 0,91–1,13), primært drevet af en øget risiko for blodprop i hjertet (HR 2,06; 95 % CI 1,21–3,52; 2 studier med 2 risikoestimater).

Disse fund stemmer overens med tidligere reviews om iskæmisk hjertesygdom, men ikke tidligere resultater hvad angår stroke. En kumulativ meta-analyse viste således øget risiko for iskæmisk hjertesygdom ved arbejde ≥55 timer/uge (RR 1,13; 95 % CI 1,02–1,26), og WHO/ILO's sygdomsbyrdeprojekt fandt tilsvarende resultater (HR 1,17; 95 % CI 1,05–1,31). Nærværende gennemgang fandt en tilsvarende risiko, men med bredere konfidensintervaller (HR 1,23; 95 % CI 0,88–1,72).

I modsætning til tidligere meta-analyser, der fandt forhøjet risiko for stroke ved lange arbejdsuger (HR omkring 1,21–1,35), fandt denne gennemgang ingen støtte for en sådan sammenhæng (HR 1,01; 95 % CI 0,87–1,16). Forskelle i inklusionskriterier forklarer sandsynligvis uoverensstemmelserne, især udelukkelse af case-control-studier med selvrapporterede udfald og inddragelsen af senere tilkomne kohortestudier af høj kvalitet.

Vigtige begrænsninger er det begrænsede antal uafhængige studier, beskedne og inkonsistente sammenhænge, mangel på detaljerede data om eksponerings-respons og mulig residual confounding.

Andre eksponeringer

Flere sjældnere undersøgte psykosociale faktorer blev også vurderet i relation til hjerte-kar-sygdom, herunder arbejdspladsressourcer, mobning, vold og seksuel chikane, forudsigelighed og utilfredshed med arbejdet. For disse eksponeringer var antallet af studier for sparsomt til at muliggøre en vurdering af årsagsmæssige sammenhænge.

DISKUSSION

I dette systematiske review anvendte vi prædefinerede, restriktive inklusionskriterier vedrørende studiedesign, definition og måling af eksponering- og sygdom samt statistisk analyse. Ud fra initialt 3.396 publikationer, identificerede vi i alt 59 relevante epidemiologiske studier publiceret mellem 1977 og 2024. I disse rapporteredes i alt 315 estimater af relativ risiko for iskæmisk hjertesygdom og/eller stroke og samlet fandtes øget risiko i relation til udsættelse for *job strain*, *effort–reward imbalance* (ERI), jobusikkerhed og ugentlig arbejdstid på mere end 55 timer.

Flere forhold har sandsynligvis ført til for lave associationer i disse studier (bias (skævvridning) mod nul, fejlagtig underestimering af risiko). For det første var begrænset eksponeringskontrast almindelig, idet kun få studier omfattede højt eksponerede populationer, og de fleste eksponeringer blev grupperet i brede kategorier, der kan sløre effekter i mere ekstreme eksponeringsgrupper. For det andet vurderede de fleste studier kun eksponering én gang ved baseline uden at tage højde for ændringer eller kumulativ eksponering i løbet af opfølgningsperioden. For det tredje kan justering for adfærdsmæssige og medicinske risikofaktorer, som muligvis ligger på stien af årsager fra eksponering til sygdom, have introduceret overjusteringsbias og dermed svækket reelle associationer. Derudover kan selektion af raske medarbejdere, især i studier af ældre studie populationer (*healthy worker selection bias*) og målefejl på grund af subjektiv fortolkning af psykosociale spørgeskemaer, yderligere have maskeret reelle effekter.

Samtidig kan andre forhold have ført til for stærke associationer i studierne (bias (skævvridning) væk fra nul, fejlagtig overstimering af risiko). De fleste eksponeringer var selvrapporterede, og der er en velkendt sammenhæng mellem ugunstig opfattelse af arbejdsmiljøet og helbredsmæssig bekymring og øget forbrug af sundhedsydelser. Dermed kan skabes en falsk sammenhæng mellem rapportering af negativt arbejdsmiljø og påvisning af ikke-fatal sygdom. Studier af årsagsspecifik dødelighed og studier med uafhængige eksponeringsmål, såsom job-eksponerings matricer, fandt generelt lavere risiko for hjertesygdom, hvilket støtter forekomst af nævnte rapporterings-bias. Lavere risikoestimater i studier baseret på job-eksponerings matricer kan dog skyldes at den individuelle eksponering måles mindre præcist og herved resulterer i bias mod nul. Confounding relateret til socioøkonomisk status er et stort problem, da uddannelse, indkomst og erhvervsstatus er forbundet både med arbejdspladseksponeringer og kardiovaskulær risiko. På trods af justering for socioøkonomiske indikatorer er residual confounding knyttet til socioøkonomisk status sandsynlig. Desuden justerede kun få studier for tidlige livsbelastninger, social isolation eller samtidige arbejdspladseksponeringer. Endelig kan publikations bias og selektiv rapportering, især i store studier med mange sammenligninger, have medført falsk høje associationer.

I betragtning af betydelig heterogenitet på tværs af studier med hensyn til populationer, eksponerings- og effektmål samt analytiske strategier, bør samlede metaanalytiske estimater ikke fortolkes bogstaveligt. I stedet giver de kun en generel indikation af den potentielle retning og størrelsesorden af sammenhænge, inden for de anerkendte begrænsninger af bias og confounding.

Psykosociale arbejdsrelaterede stressorer såsom *job strain* og *effort-reward-imbalance* er blevet forbundet med kardiovaskulære risikofaktorer såsom forhøjet blodtryk, rygning, fedme, fysisk inaktivitet og negativ blodlipidprofil. Imidlertid er der kun få undersøgelser, der rent faktisk dokumenterer mediering af en eller flere af disse faktorer. Vurdering af årsagssammenhæng i arbejdsskadesager hæmmes af den beskedne overrisiko, om nogen, og af mangel på detaljerede eksponerings-responsdata vedrørende intensitet, varighed og timing.

Forskningen har længe været domineret af demand-control-support arbejdsstress modellen, men nyere tilgange med fokus på specifikke arbejdsorganisatoriske faktorer er ved at dukke op. Disse kan give muligheder for mere objektiv eksponeringsvurdering og identifikation af modificerbare karakteristika på arbejdspladsen, der er relevante for forebyggende strategier.

SAMLET VURDERING AF KAUSALITET

Et stort antal epidemiologiske studier af høj kvalitet fra de seneste fem årtier har undersøgt sammenhængen mellem psykosociale stressorer på arbejdspladsen og risiko for hjerte-kar-sygdom. Den stærke heterogenitet i populationer og studiedesign udelukker dog mulighederne for formel konklusiv meta-analyse.

Manglende overensstemmelse af resultater på tværs af studier er oftest uden åbenlys forklaring. Associationens styrke i studier, som rapporter øget risiko er oftest begrænset. Netto-effekten af bias og konfounding er i en uforudsigelig retning. Desuden viser få studier klare eksponerings-respons-sammenhænge. Arbejdsrelaterede stressfaktorer kan bidrage til hjerte-kar-sygdomme gennem både kortsigtede og langsigtede biologiske mekanismer, men holdepunkterne for, at sådanne mekanismer medierer sammenhængene, er fortsat begrænsede.

Konkluderende vurderes evidensen for kausale sammenhænge mellem psykosociale eksponeringer og iskæmisk hjertesygdom at være begrænset for job strain, isostrain, job kontrol, social støtte, jobusikkerhed og arbejdstid på 55+ timer, mens evidensen vurderes utilstrækkelig eller uden indikationer for øget risiko for alle øvrige betragtede eksponeringer. Desuden var der begrænset evidens for, at job strain og arbejdstid på 55+ timer pr. uge kausalt er relateret til stroke. Ikke desto mindre udelukker de tilgængelige data ikke små effekter af job strain og isostrain.

* En kausal sammenhæng er mulig. En positiv sammenhæng mellem eksponering for en risikofaktor og sygdom er observeret i flere epidemiologiske studier. Det er ikke usandsynligt, at denne sammenhæng kan forklares ved tilfældighed, bias eller confounding.

ENGLISH SUMMARY

Following an open call from the Danish Work Environment Fund, an international team of researchers in occupational medicine and epidemiology summarized and evaluated the scientific evidence on causal links between psychosocial workplace exposures and cardiovascular disease. The exposures reviewed included job strain, ERI, job insecurity, and long weekly working hours, along with a range of other, rarely studied exposures. The outcomes of interest were ischemic heart disease or stroke.

METHODS

A systematic literature search was conducted in PubMed and Embase up to November 15th, 2024. The search identified 3,396 original journal articles in English that addressed associations between work-related psychosocial exposures and ischemic heart disease or stroke.

Titles and abstracts were independently screened by two authors. Based on consensus, 167 articles were selected for full-text review. Of these, 56 met à priori defined inclusion criteria: cohort and nested case-control studies addressing ischemic heart disease (including angina pectoris but not hypertension) or stroke diagnosed with medical criteria and risk estimates minimally accounting for sex, age, and at least one measure of socioeconomic status

Studies relying on individual recall of exposures after the occurrence of the outcome or using fully or partially self-reported outcomes—including self-reported physician diagnoses—were excluded.

An additional four eligible studies were identified through reference lists, bringing the total number of included studies to 59. Together, these studies contributed 315 relevant risk estimates. The coverage of the search was validated by cross-checking against original papers included in earlier systematic reviews.

We summarized risk estimates within and across studies using forest plots stratified by exposure type and main outcome group (cardiovascular disease, ischemic heart disease and stroke). If a study provided multiple risk estimates for a given exposure-outcome relationship, we calculated a single average risk estimate using inverse variance weighting. Random-effects models were applied to calculate average risk estimates across all studies regardless of statistical tests for heterogeneity. When multiple exposure levels were reported, the highest exposure level was used in the pooled estimates.

For analyses of risk by weekly working hours, we reclassified the original study categories into four groups (<35 hours/week, 35-40 hours/week, 41-55 hours/week, >55 hours/week). For each exposure type, the primary analysis assessed the overall risk of cardiovascular disease, combining ischemic heart disease and stroke, as well as risks for more specific outcomes. In supplementary analyses, we examined whether exposure-outcome associations were modified by factors such as sex, socioeconomic position, outcome specificity, independent exposure assessment, participation rate, calendar period, follow-up duration, and inclusion of potential effect modifiers in statistical models (e.g., medical and behavioral risk factors for ischemic heart disease).

RESULTS

The study base included 57 follow-up studies and two case-control studies, most of which addressed the risk of ischemic heart disease. The majority of studies were undertaken in Europe and included both general population samples and occupational samples. Information on exposure was obtained by self-report at baseline in most of the follow-up studies, but nine studies used job-exposure matrices or other independent measures of workplace exposure.

Outcomes were mostly defined by hospital discharge diagnoses or death certificates, although a minority of studies identified incident disease through clinical examinations during follow-up.

About one third of the follow-up studies enrolled participants before 1990 and participation rates were less than 75% in one third of studies. The duration of follow-up ranged from 1 to 30 years, with a median of 9.9 years. Only a minority of studies addressed highly specific outcomes such as myocardial infarction or distinguished between ischemic and haemorrhagic stroke.

The demand-control-support (DCS) work stress model proposes that job strain- defined as the combination of high job demands (in terms of workload and time pressure) and low job control (in terms of limited decision authority and skill discretion) - increases the risk of adverse health effects. Additionally, high levels of workplace social support are hypothesized to buffer the adverse effects of job strain. This combination of high demands, low control, and low support is referred to as isostrain, with "iso" denoting isolation. The model implies that the effect of job strain arises from the interaction between demands and control, independent of their individual effects. In its full form, the model also assumes that job strain interacts with social support.

We identified a total of 25 follow-up studies and one case–control study examining the association between job strain and cardiovascular disease, providing 49 risk estimates. Most studies were conducted in Europe and included both general population and occupational samples. Sample sizes ranged from approximately 1,500 participants to several million.

The primary outcome was ischemic heart disease, while only a few studies addressed stroke or cardiovascular mortality. Job strain was typically assessed by combining measures of job demands and control, most often dichotomized at the median—either versus all others or versus the low-demand/high-control group. Exposure data were mainly obtained through self-report.

Pooled analyses showed associations between job strain and cardiovascular disease after full adjustment. The average variance-weighted hazard ratios (HRs) were 1.13 (95% CI 1.06–1.21, 26 studies with 49 risk estimates) for cardiovascular disease overall, 1.14 (95% CI 1.06–1.23, 21 studies with 32 risk estimates) for ischemic heart disease, and 1.19 (95% CI 1.03–1.37, 7 studies with 13 risk estimates) for stroke.

There were indications of higher risk in studies conducted outside the Nordic countries, among blue-collar workers, and in studies relying on self-reported exposure data. Associations were stronger in analyses that did not adjust for behavioral and medical risk factors. In contrast, studies using job exposure matrices reported weaker associations. Sex did not consistently modify the observed associations. Two studies examined time-varying exposure and found associations with both current and cumulative job strain.

Iso-strain, the combination of low social support and job strain, was linked to cardiovascular disease overall the in meta-analysis (HR 1.21, 95% CI 1.06-1.38, 4 studies with 9 risk estimates). However, results across individual studies were conflicting. High job demands, low job control and social support were each associated with cardiovascular disease (meta-analytic HR 1.02, 95% CI 0.96-1.09, 19 studies with 35 estimates; HR 1.03, 95% CI 1.03-1.12, 24 studies with 47 estimates; HR 1.10, 95% CI 1.00-1.21, 9 studies with 18 estimates). There was no evidence for exposure-response relationships for any of these exposures.

The findings are consistent with those of eleven earlier systematic reviews, including two reviews of reviews.

Key issues affecting causal inference include substantial heterogeneity across studies, the small magnitude of observed associations, and limited or absent evidence of exposure–response relationships. Additionally, the potential for net bias is unpredictable, as some sources of bias may attenuate risk estimates while others may inflate them. A further limitation is the lack of confirmation of findings using independently assessed exposure measures and lacking adjustment of job strain and isostrain by the basic components of the DCS model. Finally, publication bias seems to be an issue with respect to job strain,

The effort-reward imbalance (ERI) model posits that high work effort paired with low rewards leads to adverse health outcomes which are amplified by a personal characteristic, overcommitment to work. Again, the effects of ERI are understood to result from the interaction between effort and reward, independent of the separate effects of the individual components of the model.

Three follow-up studies with six risk estimates examined perceived ERI and the risk of ischemic heart disease. These included the Whitehall study of civil servants in London, a study of eleven European cohorts addressed by the IPD-Work Consortium, and a study of Canadian white-collar employees. An additional study exclusively addressed effects of overcommitment. Different self-reported measures of ERI were used, mainly based on the effort/reward ratio dichotomized as > 1.0 versus ≤1.0. No studies examined the risk of stroke in relation to ERI.

All studies consistently found that ERI was associated with ischemic heart disease overall (average meta-analytic HR 1.18, 95% CI 1.03–1.35, 3 studies with 4 risk estimates), though without clear exposure-response patterns. One study reported an association only among men. Associations with ischemic heart disease were noted for high effort and low reward analysed separately (meta-analytic HR for two studies with two estimates: high effort 1.07, 95 % CI 0.85-1.36; low reward HR 1.11, 95% CI 0.92-1.34).

No studies assessed interactive effects of effort and reward on the risk of ischemic heart disease. One study found no evidence that overcommitment amplified the effects of ERI. The IPD-Work Consortium study reported an association between ERI and ischemic heart disease that was independent of job strain. No studies investigated the association between ERI and stroke.

One earlier systematic review concluded that the evidence on associations between ERI and ischemic heart disease is limited, but newer studies which were not included in that review support an association.

Key issues for causal inference are crude exposure assessment performed at a single occasion at baseline, lack of comprehensive data on exposure-response, small risk elevations susceptible to residual confounding, and lack of adjustment for effects of effort and reward in two of the three studies addressing ERI.

Job insecurity - defined as the fear of losing one's job, uncertainty about continued employment, or being employed in a company undergoing downsizing - has been hypothesized to increase the risk of cardiovascular disease. Proposed mechanisms include psychological distress, disturbed sleep, and biological stress responses.

Six prospective studies examined perceived job insecurity in relation to ischemic heart disease, while two studies assessed cardiovascular outcomes following workplace downsizing or organisational change. Across the six studies on perceived job insecurity, the weighted average risk for ischemic heart disease was HR 1.16 (95% CI 1.05–1.28). The largest of these, conducted by the IPD-Work Consortium, reported a fully adjusted hazard ratio for myocardial infarction of 1.05 (95% CI: 0.90–1.24).

Earlier cohort studies reported higher risk estimates (HRs ranging from 1.19 to 2.50), although few reached statistical significance. Only one study addressed stroke, and it found no association with job insecurity.

. A Finnish register-based study found no increase in ischemic heart disease mortality following downsizing and a Danish study suggested an elevated risk of cardiovascular disease after organisational restructuring. Of notice, another Finnish register-based study reported a twofold increase in cardiovascular mortality in relation to downsizing, but this otherwise eligible study was excluded, because the outcome was not restricted to ischemic heart disease and/or stroke.

Earlier systematic reviews have concluded that there is limited to modest evidence linking job insecurity to coronary heart disease. Socioeconomic factors and health behaviors likely contribute to the observed associations.

Key limitations for causal inference include crude exposure assessments, lack of exposure–response analyses, and potential confounding by psychological or social factors, which may bias results in unpredictable directions. Findings from studies on downsizing and organisational restructuring have also been inconsistent.

Long weekly working hours have been hypothesized to increase the risk of cardiovascular disease through several pathways. These include excessive fatigue, insufficient recovery, reduced sleep duration, lower levels of leisure-time physical activity, social isolation, competitive personality traits, and unhealthy behaviors such as poor diet.

Nine epidemiological studies examined the association between long weekly working hours and cardiovascular disease, providing 54 risk estimates across different levels of working hours, outcomes, and population subgroups. Exposure was self-reported in all studies except one case–control study, which partially relied on salary records to determine working hours.

Compared to standard hours (35–40 hours/week), working 40–55 hours per week was not associated with an increase in the risk of cardiovascular disease overall (meta-analytic HR 1.02, 95% CI: 0.93–1.12). For those working 55 hours or more per week, there was a small, non-significant increase in the overall risk of cardiovascular disease (HR 1.09, 95% CI: 0.91–1.13), primarily driven by an elevated risk of myocardial infarction (HR 2.06, 95% CI 1.21-3.52, 2 studies with 2 estimates).

These findings align with earlier reviews on ischemic heart disease but diverge with respect to risk of stroke. A cumulative meta-analysis reported an increased ischemic heart disease risk among employees working ≥ 55 hours weekly (RR 1.13, 95% CI 1.02–1.26), and similar results were found in the WHO/ILO burden of disease project (HR 1.17, 95% CI 1.05–1.31). The present review found a comparable risk for ischemic heart disease, but with broader confidence limits (HR 1.23, 95% CI 0.88–1.72), reflecting heterogeneity between studies.

In contrast to earlier meta-analyses that reported elevated stroke risks for long working hours (HRs around 1.21–1.35), the current review did not find evidence supporting this association (HR 1.01, 95% CI: 0.87–1.16). Differences in inclusion criteria likely explain the divergence, particularly the exclusion of several case–control studies with self-reported outcomes and the inclusion of more recent high-quality cohort studies in the current review.

Key limitations for causal inference include the limited number of independent studies, modest and inconsistent associations, lack of detailed exposure–response data, and potential residual confounding.

Other exposures. Several less commonly studied psychosocial workplace factors have been investigated in relation to cardiovascular outcomes including workplace resources, work-related bullying, violence and sexual harassment, predictability and job dissatisfaction. For these exposures, the number of available studies was too sparse to allow causal inference.

EVIDENCE SYNTHESIS

In this systematic review, we applied predefined, strict inclusion criteria regarding study design, exposure and outcome ascertainment, and statistical analysis. A total of 59 eligible epidemiological studies published between 1977 and 2024 were identified. Across 315 relative risk estimates, there were indications of increased risk of ischemic heart disease and stroke associated with job strain, effort–reward imbalance, job insecurity, and weekly working hours exceeding 55 hours.

Several factors likely biased associations towards the null. First, limited exposure contrast was common, with few studies targeting highly exposed populations, and most exposures were grouped into broad categories that may obscure effects in more extreme exposure groups. Second, most studies assessed exposure only once at baseline, without accounting for changes or cumulative exposure during follow-up. Third, adjustment for behavioral and medical risk factors which may be on the causal path from exposure to the outcome may have introduced overadjustment bias and thus attenuated true associations. Additionally, healthy worker selection, particularly in studies recruiting older employees, and measurement error due to subjective interpretation of psychosocial questionnaires may have further masked real effects.

At the same time, sources of bias may have inflated risk estimates. Most exposures were self-reported, and unfavorable perceptions of the work environment may be linked to adverse health concerns and greater healthcare utilization, potentially influencing detection of non-fatal outcomes. Cause-specific mortality studies and studies using independent exposure measures, such as job exposure matrices, generally found lower risks, supporting concerns about reporting bias although it is acknowledged that such measures may less accurately capture the individual exposure and hereby result in bias towards the null. Residual confounding by socio-economic status is a major concern, as education, income, and occupational status are linked both to workplace exposures and cardiovascular risk. Despite adjustment for socio-economic indicators, residual confounding likely persisted. Furthermore, few studies adjusted for early life adversity, social isolation, or co-occurring workplace exposures, limiting the control of confounding. Finally, publication bias and selective reporting, particularly in large studies with multiple comparisons, may have exaggerated associations.

Given substantial heterogeneity across studies in terms of populations, exposure and outcome measures, and analytical strategies, pooled meta-analytic estimates should not be interpreted literally. Instead, they provide a general indication of the potential direction and magnitude of associations, within the acknowledged limitations of bias and confounding.

Psychosocial stressors such as job strain and ERI have been associated with cardiovascular risk factors such as hypertension, smoking, obesity, physical inactivity and adverse blood lipid profiles. However, studies that actually document mediation by one or more of these factors are sparse. Assessment of causality in litigation cases is hampered by the modest excess risk, if any, and by lack of detailed exposure-response data regarding intensity, duration, and timing.

Research has long been dominated by the demand–control-support model, but newer approaches focusing on specific work organisational factors are emerging. These may offer opportunities for more objective exposure assessment and identification of modifiable upstream workplace characteristics relevant for preventive strategies.

OVERALL EVALUATION OF THE EVIDENCE

A large body of high-quality epidemiological studies from the past five decades addresses links between psychosocial stressors at the workplace and cardiovascular risk. The strong heterogeneity of populations and study designs precludes options for formal meta-analysis.
Many studies show unresolved inconsistencies. Where risk estimates are elevated, they tend to be small or modest in magnitude. In addition, there is a likely risk of bias and confounding, with a net effect in an unpredictable direction. Furthermore, few studies demonstrate clear exposure-response relationships. Work stressors may contribute to cardiovascular disease through both short and long-term biological mechanisms but evidence that such mechanisms mediate the associations remain limited.

In conclusion, the evidence for causal links between psychosocial exposures and ischemic heart disease was considered limited* for job strain, isostrain, job control, social support, job insecurity and working 55+ hours, while the evidence was without indications for increased risk or insufficient for all other considered exposures. Moreover, there was limited evidence that job strain and working 55+ hours per week is causally related to stroke. Nonetheless, the available data do not rule out small effects of job strain and isostrain.

*A causal relationship is possible. A positive relationship between exposure to a risk factor and outcome has been observed in several epidemiological studies. It is not unlikely that this relationship can be explained by chance, bias or confounding.

INTRODUCTION

Ischemic heart disease and stroke account for the majority of all cardiovascular diseases [1]. Despite a marked decline in mortality in ischemic heart disease over the past 40 years, cardiovascular diseases remain a leading cause of morbidity and mortality worldwide [1, 2] even though the favourable trend in ischemic heart disease mortality appears to be levelling off [3].

The risk of ischemic heart disease and stroke increases exponentially with age and is higher in men. In Denmark, the incidence of first-time myocardial infarction decreased in men from 243 per 100,000 in 2005 to 174 per 100,000 in 2021, and in women from 143 to 80 [4]. The incidence of first-time ischemic stroke in the Danish population was 2.70/1000 person-years in 1996 and a little lower in 2016 (1.99/1000 person-years), higher in men than in women [5].

There is a pronounced inverse social gradient in the occurrence of ischemic heart disease and stroke [6, 7], only partially explained by established medical, physiologic and behavioural risk factors. These include hypertension, hypercholesterolemia, diabetes, smoking, low leisure time physical activity and obesity [8, 9].

In addition to conventional risk factors, several psychosocial stressors—both acute and chronic—have been linked to increased cardiovascular risk. These include episodic events such as job loss, natural disasters, bereavement, and emotionally intense sports events, as well as more persistent conditions like unemployment, social isolation, and serious illness in close family members [10].

Psychosocial factors are poorly defined in occupational epidemiology [11]. In this report, the term refers both to psychological demands placed on workers (e.g., workload, time pressure) and the social context of work (e.g., influence on work task, supervisor support, interpersonal relations, job insecurity). It also includes up-stream organisational factors such as long working hours that potentially may impact the psychosocial work environment.

The association between a wide range of work-related psychosocial exposures and cardiovascular disease has been the focus of occupational epidemiology for more than 50 years, as reflected in a growing body of literature, including several reviews [12-27], two meta-reviews [28, 29] and consensus statements [30, 31].

Among these exposures, job strain—defined according to the job demand–control model by Robert Karasek in the late 1970s—is by far the most studied [17, 20, 21, 25]. Fewer studies have examined other exposures, such as effort–reward imbalance [22], job insecurity [16], and long working hours [23]. Evidence on additional exposures—such as organisational injustice, sexual harassment, bullying, violence, predictability, and workplace resources—remains limited.

Although several reviews provide evidence for associations between psychosocial work factors and risk of ischemic heart disease and stroke, it remains uncertain whether associations are causal [32-37]. Most studies rely on self-reported assessments of psychosocial exposures, which may imply a risk of false associations or that an association appears stronger than it is [38]. Moreover, such data may lack comparability across populations and social groups [33]. The relative risks often reported may also be inflated by residual confounding from unmeasured determinants such as socioeconomic factors that are not fully accounted for, early adversity, psychiatric morbidity and poor social network [34, 36, 37, 39, 40] – factors that rarely are considered.

Other unresolved issues include the need to clarify exposure–response relationships and to disentangle independent versus interacting effects of various exposures. In particular, there is a need to clarify whether the effect of job strain, if any, is due to the combination of high demands and low job control (interaction) – as often assumed – or if the association is driven by independent effects of high job demands and/or low job control [41]. In particular the latter is susceptible to social confounding, for example by socioeconomic position. Similarly, effects of ERI may be confounded by efforts and demands if these main effects are not accounted for [42].

This systematic review was commissioned by the Danish Work Environment Fund to provide an updated knowledge base to support decision-making regarding whether—and to what extent—specific workplace psychosocial exposures contribute to cardiovascular disease. In addition to include findings from numerous recent original studies [43-60], this review focuses exclusively on follow-up studies and case-control studies with objective and independent exposure assessment - considered most informative for causal inference. Particular attention is given to exposure-response relationships, residual confounding, bias inflating as well as attenuating risk estimates, potential modifying effects of socio-economic position and insights obtained from studies applying independent or objective measures of exposure.

OBJECTIVES

(1) To summarize and evaluate the epidemiological and medical evidence for the risk of cardiovascular disease resulting from work-related psychosocial exposures. Cardiovascular diseases include ischemic heart disease and stroke. Psychosocial exposures encompass job strain (with main dimensions), ERI (with main dimensions), long weekly working hours, job insecurity, organisational justice, workplace resources, predictability, unfairness, job satisfaction, work-related bullying, violence, threats, and harassment.

(2) To quantify disease risk in relation to intensity, and duration of specific exposures (exposure-response) and to assess consistency across studies, including a focus on studies with exposure metrics independent of individual reporting.

(3) To clarify to what extent the basic dimensions of the job strain model (specifically psychological demands, job control, and social support) and the ERI model (effort, reward, and overcommitment) underlie combined (interactive) effects.

(4) To compare disease risk associated with specific exposures across gender and socio-economic groups.

METHODS

The protocol was published by the international prospective register of systematic reviews (Prospero) at the initial stage of the research before completion of the literature search [61].

Literature search

We conducted a systematic literature search to identify all original peer-reviewed papers in English that provide estimates of associations between work-related psychosocial exposures and cardiovascular disease (ischemic heart disease and/or stroke). The search was carried out in **PubMed** on November 15, 2024 (covering publications from 1966 onward), and in **Embase** on November 16, 2024 (covering publications from 1947 onward).

Search strings were developed in PubMed based on criteria used in previous systematic reviews. These combined Medical Subject Headings (MeSH) and keyword terms related to study design, occupational exposures, and cardiovascular outcomes. The final search syntax was then translated to Embase format. To validate the search strategy, we verified whether original studies included in earlier systematic reviews of key exposure types were retrieved [16, 20, 21, 23-25, 62, 63]. After refining and updating the search strings, the final search captured all 77 original papers referenced in those reviews. In total, the search yielded 3,396 articles, including 652 from Embase. Annexes II and III provide details.

Two authors (SS and JPB) independently screened titles and abstracts for eligibility using the **Covidence** platform [64]. After resolving 60–70 initial discrepancies through discussion, consensus was reached to include 166 articles for full-text review. Applying predefined inclusion and exclusion criteria listed below, 112 of these articles were excluded. The remaining 55 original studies were retained following consensus among three authors (JPB, SM, and SS), ensuring that each paper had been reviewed by at least two researchers.

An additional four eligible papers were identified through reference lists, bringing the total number of included original studies to 59 (see Annex IV for full list). A list of excluded articles, along with specific reasons for exclusion, is provided in Annex V.

Inclusion criteria:

(1) Original epidemiological studies providing quantitative risk estimates with confidence intervals for associations between work-related psychosocial exposures and ischemic heart disease and/or stroke.
(2) Study design: Cohort and nested case-control studies with outcome data collected independently of exposure data. Hospital-based case-control and cross-sectional studies were considered less informative due to potential recall bias but were included if exposure data were collected independently of outcomes (e.g. studies using objective exposure metrics).
(3) Outcome: Ischemic heart disease (ICD-8-9: 410-414; ICD-10: I20-I25, including angina pectoris but not hypertension) and/or stroke (ICD-8-9: 430-434, 436; ICD-10: I61-I65, including ischemic and haemorrhagic stroke), see Annex VIII for details. The diagnosis should be based on medical criteria such as hospital discharge diagnoses, death certificates, or clinical examination. Hypertension is not embraced by the mentioned ICD codes. Studies providing combined risk estimates for ischemic heart disease and stroke, without separate estimates for each disease, were included.
(4) Risk estimates minimally adjusted for sex, age, and at least one measure of socioeconomic status (e.g., income, education, occupation, or employment grade) through analysis, stratification, or study design.

Exclusion criteria:

(1) Participants with prevalent or previous evidence of outcome conditions at baseline.
(2) Exposure data based on individual recall after the occurrence of the outcome.
(3) Fully or partially self-reported outcomes, including self-reported physician diagnoses.
(4) Studies with overlapping populations and analyses, where only the most recent or most informative study was included.
(5) Studies with selective reporting of results in relation to the stated objectives.

Data Extraction

For each included article, information was systematically extracted using a predefined template and entered into external data files. These files were used for tabulation, graphical visualization of risk estimates (forest plots), and statistical calculations. Extracted variables included demographic characteristics and a wide range of study-specific information: study population, study design, definitions and assessments of exposure and outcome, statistical analysis and potential confounders.

Both estimates minimally adjusted for sex and age (if available) and fully adjusted estimates (at least also including a measure of socioeconomic position) with 95% confidence intervals were extracted. We retrieved estimates for all reported exposure levels (e.g., defined by medians or tertiles of questionnaire scores), outcomes (e.g., overall stroke, ischemic and haemorrhagic stroke), and subgroups (e.g., sex and occupational groups). As cardiovascular outcomes are comparatively rare in people of working age, we treated relative risks (RRs), hazard ratios (HRs), and odds ratios (ORs) as equivalent. To ensure comparability across studies, risk estimates were inverted when necessary, so that all exposures were aligned in the same direction – i.e., towards increasing the risk. For example, protective effects of high job control or high rewards were reversed to reflect elevated risk. However, estimates for intermediate exposure levels could not be inverted and were left out from the meta-analyses.

We also recorded whether analyses accounted for specific potential confounders and modifiers (yes/no) and noted other factors related to bias and causal inference: baseline participation rate, loss to follow-up, independent exposure measurements, specificity of outcomes, cumulative exposure metrics, timing of outcomes relative to exposure, exposure-response analyses, and analyses of interaction between different psychosocial exposures.

Data Synthesis and Statistical Analysis

We summarized risk estimates within and across studies using forest plots, stratified by exposure type. If a study provided multiple risk estimates for a specific exposure-outcome relationship, we calculated a fixed-effect inverse variance weighted average risk estimate using the *metafor* package (REML option) in R software (R Foundation for Statistical Computing, Vienna, Austria). Examples are studies only providing risk estimates stratified by gender, age or occupational grade. This ensured that each study contributed only one risk estimate to the pooled analysis.

For meta-analyses across studies, we applied random-effects models regardless of statistical tests for heterogeneity, as populations, exposure definitions, and measurement units varied across studies. Again, to prevent bias from multiple estimates per study, only the highest level of exposure was used in the pooled analysis, ensuring one effect estimate per study. Risk estimates for all levels of exposure are provided in Annex VI. Potential publication bias was assessed by visual inspection of funnel plots with asymmetry suggesting possible bias.

Several papers from the IPD-Work Consortium included data from multiple unpublished cohorts. For these studies, we computed a weighted random-effects average with confidence intervals. Cohorts published separately (e.g., the Whitehall study on job insecurity [65], also included in [16]) and those that did not meet our inclusion criteria were excluded from these calculations.

For studies addressing weekly working hours, we reclassified original exposure categories into four groups (<35 h/week, 35-40 h/week, 41-55 h/week, >55 h/week). All studies except one used 35-40 h/week as the reference category. Due to variation in how studies categorized the 41–55-hour range, all risk estimates in this group were combined into a single category. See Annex VI-4 for details.

For each exposure type, the primary analysis assessed the overall risk of cardiovascular disease (aggregating ischemic heart disease and stroke), as well as risk reported in mortality studies and risk of more specific outcomes such as myocardial infarction or ischemic stroke. In supplementary analyses, we assessed whether exposure-outcome associations varied by a range of characteristics such as sex, socioeconomic position, outcome specificity, use of independent exposure assessment, participation rate, calendar period, follow-up duration, and inclusion of potential effect modifiers in statistical models (e.g., medical and behavioural risk factors for ischemic heart disease). Finally, meta-analyses were repeated leaving out the results of the two case-control studies.

RESULTS

Characteristics of included studies

The study base included 57 follow-up studies, and two case-control studies published from 1977 through 2024, yielding a total of 315 risk estimates, most of which related (Table 1a). The majority of studies were undertaken in Europe, in particular the Nordic countries, and addressed both general population and occupational samples. Only a few studies focused exclusively on male or female populations or on specific occupational groups (e.g., nurses, white- or blue-collar workers).

Information on exposure was obtained by self-report at baseline in the majority of the follow-up studies, but 16 studies used job-exposure matrices or other independent measures of workplace exposures. Outcomes were mostly identified by hospital discharge diagnoses or death certificates, while only few studies used clinical examinations during follow-up to detect incident diseases.

About one third of the follow-up studies enrolled participants before 1990 and participation rates among eligible were less than 75% in one third of studies. The duration of follow-up spanned between one and 30 years (median 9.9 years). The number of incident cases was less than 500 in 55% of studies and exceeding 1000 in 25% of studies. Only a minority of studies addressed highly specific outcomes such as myocardial infarction or distinguished between ischemic and haemorrhagic stroke. Still, haemorrhagic stroke represents a minority of all stroke cases in the countries represented here, and the findings, accordingly, will mostly apply to ischemic stroke.

The most frequently studied exposures were job strain and its main components, long weekly working hours and job insecurity. A range of other exposures including ERI were addressed in only few studies that met the inclusion criteria for this review (Table 1b). The majority of studies relied on a single measurement of exposure, with only two studies evaluating cumulative exposure over time. Although many studies adjusted risk estimates for a range of behavioural and medical determinants of ischemic heart disease and stroke, only few accounted for other established risk factors such as family history of cardiovascular disease, childhood adversity or social isolation (Table 1c).

The job demand-control-support model

Introduction. In the late 1970s, Robert Karasek introduced the demand-control-support (DCS) work stress hypothesis, proposing that job strain - defined as the combination of high job demands and low job control - increases the risk of adverse health effects [66]. Job demands referred to workload and time pressure and job control (also labelled decision latitude) referred to decision authority and skill discretion. Later, it was hypothesized that high workplace social support may buffer the adverse effects of job strain. This extended model, incorporating low social support, is known as “iso-strain”, with *iso-* referring to isolation [67].

The JC hypothesis implies, that effects of job strain result from an interaction between demands and control independent of the separate effects of demand and control [68], and – in the full model – that job strain interact with social support.

Various versions of the self-administered Job Content Questionnaire (JCQ) have been used to assess the three dimensions of the JC hypothesis. Responses are typically measured on Likert-type scales and analysed by creating mean scores for each dimension. These scores are then grouped - most often by medians or tertiles—to define exposure categories and their combinations.

Studies. We identified 25 eligible follow-up studies and one case-control study on *job strain* with a total of 49 risk estimates of cardiovascular disease, including cardiovascular mortality (Table 2a). Twenty-one of these studies addressed ischemic heart disease, 11 of which specifically reported on myocardial infarction. Only six studies investigated stroke and just two studies reported on ischemic heart disease and stroke combined.

The most common method for exposure assessment was the use of self-administered questionnaires at baseline. A list of items representing the various dimensions of the original JC model is provided in Annex VII. Most studies used abbreviated or adapted versions of the original Job Content Questionnaire (JCQ) [38,39], often with modified items or response options [40]. Where reported, internal consistency (e.g., Cronbach’s alpha) for the subscales on demands, control, and social support was typically above 0.65, though exceptions existed [41,42]. Factor analyses, such as one conducted in a large French population, largely confirmed the JCQ’s dimensional structure [38].

Nine studies applied job exposure matrices or other independent sources for assessment of exposure. Only three studies provided repeated or cumulative measures of exposure over time [43, 69, 70]. In nearly all studies, job strain was defined by combining scale scores for job demands and job control, both dichotomized at the median. Job strain was in analyses contrasted with either low strain (sometimes labelled the 'relaxed' group of the demand-control quadrant, 12 studies), all other (the three other quadrants: active, passive and relaxed, five studies) or alternative ways of grouping (three studies). Only one study assessed exposure–response for job strain as a composite measure [46].

Associations between *job demands* and cardiovascular disease were examined in 19 studies providing a total of 50 risk estimates (Table 1b). For *job contro*l was addressed in 24 studies (58 risk estimates) and *social support* in nine studies (23 risk estimates). Unlike job strain, risk estimates were often provided by tertiles or quartiles of scale scores enabling trend analyses. Such analyses were reported in 13 studies for job demand and 12 studies for job control. *Iso-strain* was examined in four studies (9 risk estimates).

Results

Job strain. After pooling of within-study risk estimates, the weighted random-effect risk estimate across all studies was elevated for cardiovascular disease, ischemic heart disease and stroke without obvious indications of outcome specificity and with broad confidence intervals (Figure 1a, Table 2a). Analyses of risk of cardiovascular disease in subgroups indicated higher risk in non-Nordic countries, occupational samples, in blue-collar workers, in studies with self-reported exposure and in studies with low response rates, small sample sizes, non-registry-based outcomes and long follow-up (Table 3a). The risk of cardiovascular disease seemed not to be modified by sex. Thus, fifteen studies conducted stratified analyses by sex or included only one sex, but there was no consistent evidence suggesting that sex modified the association between job strain and risk of cardiovascular or ischemic heart disease (Tables 3a and 3b). Findings of risk in subgroups were remarkably similar in analyses addressing ischemic heart disease and cardiovascular disease (Table 3a and 3b). One of the 26 studies was a large case-control study using a survey-based job exposure matrix [71]. Findings in this study were close to the average results of the cohort studies (Figure 1a).

Overall, meta-analytic risk estimates that included full adjustment for confounders were attenuated compared to minimally adjusted estimates (Table 3a). Four studies of job strain and cardiovascular disease examined the multiplicative interaction between high job demands and low job control [72-75]. None of these found significant associations between job strain (the product term in the model) and cardiovascular disease. In studies using the quadrant method, job strain was not adjusted for the independent effects of demands and control.

In seven studies that used survey-based or expert-rated job exposure matrices for exposure assessment, the estimated risk of cardiovascular disease and ischemic heart disease was on average between one-half and one-third of that observed in studies using individual self-reports of exposure (Tables 3a and 3b). However, findings based on job exposure matrices were heterogeneous. One study found increased risk of myocardial infarction among male blue-collar workers but not among white-collar workers [76]. Another found short- and long-term effects in an occupational sample, which disappeared after adjusting for education [70]. Five other studies did not report significant associations between job strain and ischemic heart disease [43, 72, 75, 77, 78].

Four other studies did not find significant associations between job strain and cardiovascular disease or mortality [43, 72, 77, 78].

With two notable exceptions, no studies evaluated effects of cumulative exposure or the timing of exposure relative to disease onset. The first exception is a French study on cardiovascular mortality, in which job strain was assessed annually from 1976 to 2002 using a survey-based job exposure matrix [43]. Cumulative job strain across all years was associated with IHD in men (HR 1.24, 95% CI 1.04-1.48) but not in women (HR 1.04, 95% CI 0.65-1.67). Similar effects were observed for current exposure and a measure of cumulative exposure giving more weight to recent exposure. However, effects were not adjusted by job demands and decision latitude, and the latter may have confounded the effect of job strain. Adjustment for socio-economic class was by various job exposure matrix derived chemical and physical exposures rather than by income or education.

The second exception is a large Danish cohort study examining risk of fatal and non-fatal myocardial infarction in an occupational sample using a sex-, age-, and calendar-year-specific survey-derived job exposure matrix [79]. Job strain at baseline was associated with increased risk throughout the follow-up period, and risk estimates were higher when high job strain was defined using quartiles (adjusted HR 1.24, 95% CI: 1.19–1.29) rather than medians (adjusted HR 1.07, 95% CI: 1.03–1.10). Additional analyses of changes in job strain year-to-year indicated increased risk of ischemic heart disease following both the onset (HR 1.20, 95% CI: 1.12–1.29) and cessation (HR 1.20, 95% CI: 1.12–1.28) of job strain compared to persistent low strain. Socioeconomic position was adjusted for by income, and with further adjustment for education, the association with baseline exposure disappeared. No elevated risk was observed with a higher number of exposed years; if anything, data suggested the opposite.

Isostrain was examined in four studies with nine risk estimates. Meta-analysis indicated an association between high levels of isostrain and cardiovascular disease (Table 2a, Figure 2). However, findings of the studies were conflicting. The Belstress cohort of employees in a range of private and public industries revealed a substantially increased risk of ischemic heart related to high baseline isostrain. The outcome was defined by various clinical endpoints including unstable angina pectoris [80]. Analyses of multiplicative interaction between demands, control and social support were not provided. However, stratified analyses indicate that associations were driven by social support. These results were only partly consistent with findings in a large French mortality study, which reported increased cardiovascular disease mortality in women but not men [43]. Moreover, no increased risk for cardiovascular disease mortality was observed over twelve years of follow-up in a Swedish cohort of county residents (average age 49 years) [74], nor in a separate cohort of Swedish residents in the Malmö area [81].

Job demands, job control and social support. Across all studies, the highest exposure level of *job demands,* and the lowest level of *job control* and *social support* were associated with increased risk of cardiovascular disease. These associations showed no clear outcome specificity, and with few exceptions, confidence intervals included unity (Table 2a, Figure 3-5).

Subgroup analyses revealed risk estimates similar to those observed for job strain (data not shown). If anything, the relative risk of cardiovascular disease appeared higher in occupational samples and in studies with small sample sizes, self-reported exposure, low response rates, and (for job demands) in white-collar workers. No consistent differences were found by sex.

In ten studies, job demands, and job control were grouped into tertiles or quartiles, allowing assessment of exposure–response relations. For job demands, risk increased monotonically across tertiles in five studies, though none reported statistically significant trend tests (Figure 3). No consistent exposure–response relationships were found for job control or workplace social support (Figures 4 and 5).

Earlier reviews. The findings of this review are consistent with those of eleven earlier systematic reviews published since 1999, including five meta-analyses. With the exception of one review, which focused on coronary heart disease mortality [25], all reviews concluded that the evidence supports an association between job strain and ischemic heart disease. However, several of these reviews highlight limitations related to study design and exposure assessment, and only one explicitly judged the evidence for causality to be sufficient [82].

As the number of large cohort studies has grown, the strength of observed associations appears to have diminished [83, 84]. Regarding high job demands and low job control—factors for which this review found weak associations with cardiovascular disease—the conclusions of prior reviews are less consistent. Some have suggested that the relative importance of these measures may shift over time, and that job demands in particular may be perceived and reported differently by white-collar and blue-collar workers [85].

Over a decade ago, it was argued that further replication of cohort studies on the cardiovascular effects of job strain was unnecessary, and that future research should focus on intervention studies to establish causality [62]. To date, however, no intervention studies have been published, underscoring the substantial challenges involved in designing and conducting such studies.

Consistency, bias and confounding. Recent epidemiological research addressing cardiovascular effects related to the JC work stress model has provided insight into at least three important sources of bias. First, the IPD-Work Consortium has, through analyses of unpublished data from a several occupational cohorts, demonstrated that publication bias is an issue as the job strain related risk of ischemic heart disease was lower in unpublished cohorts. The funnel plot of studies included in this review is also indicative of publication bias (Figure 1b). Accordingly, the potential adverse effects of job strain may seem less than earlier anticipated [83].

Second, the vast majority of earlier studies only assess exposure at the beginning of follow-up, failing to account for changes over time. One large study has provided evidence that effects may occur within one to two years following a change in exposure, suggesting short-term or triggering effects of job strain - though findings are not entirely consistent [70]. Ignoring the timing and duration of exposure may reduce the likelihood of detecting true associations, particularly in studies with a single baseline measurement and extended follow-up periods, which represent the majority of research to date.

Third, several studies using job exposure matrices have failed to replicate evidence based on individual-level assessment of exposure [43, 70, 72, 75-78]. When job exposure matrices do not accurately reflect the average exposure within an occupation, the resulting non-differential misclassification biases risk estimates toward the null [86, 87]. Furthermore, the potential information bias introduced by individual assessment of exposure is not eliminated by job exposure matrices derived from population surveys with questionnaires. The implication is, that job-exposure-matrix derived estimates may also be inflated. Only one study used a job exposure matrix based on expert ratings and found no association between job strain and myocardial infarction or ischemic heart disease mortality [75]. Of note, a job exposure matrix may not capture the relevant areas of work that are related to health, and people's own reports could be more accurate.

Despite scientific progress, some bias-issues related to the JC work stress model remain unresolved. First, only four studies examined the effect of job strain while accounting for the separate effects of job demands, job control, and social [72-75]. None of these found significant associations between job strain (the product term in the model) and cardiovascular disease. However, other researchers have addressed the issue of combined effects of high job demands and low job control by stratified analysis of combinations of median split dichotomies of job demands and job control (often referred to as 'the quadrant method'). Thus, the IPD-Work Consortium compiled data on risk of myocardial infarction in 13 European cohorts according to these categories [88]. Using the group with high control and low demands as the reference group, the hazard ratio was 1.12 (95% CI 0.99– 1.27) for low demands and low control, 1.06 (95% CI 0.94–1.19) for high demands and high control, and 1.28 (95% CI 1.11–1.48) for high demands and low control (job strain) [89], indicating that the combination of high demands and low control (job strain) produces the most robust effect compared with each of these factors alone. These risk estimates were only adjusted for sex and age. In a revised analysis from 2019, risk estimates were also adjusted for socioeconomic class [90]. The revised median split quadrant hazard ratios were 1.07 (95% CI 0.90-1.27) for the combination of low demands and low control, 1.09 (95% CI 0.97-1.23) for high demands and high control and 1.21 (95% CI 1.05-1.39) for high demands and low control (job strain). From the revised numbers the expected hazard ratio of the combined independent effect of demands and control would be approximately 1.09 x1.07=1.17, close the estimated hazard ratio of job strain assuming multiplicative interaction. Furthermore, when also considering the findings from the four studies that included formal statistical tests for interaction using multiplicative models [25-28], it remains unclear whether the observed effects of job strain are primarily driven by one or more of its specific components. This uncertainty has important implications for both interpretation and practical application. Second, considering the limited magnitude of effects observed in the majority of more recent follow-up studies, residual confounding is an issue – not the least because only few studies adjust for strong social antecedent determinants [91]. Finally, exposure-response data on effects of job strain are still largely missing.

Summary of key points. In total 26 high quality cohort studies indicate on average a slightly increased fully adjusted risk of ischemic heart disease and stroke for job strain, but with strong heterogeneity across studies. Data on exposure-response relationships are large lacking. Most JEM based studies do not corroborate findings in studies based on self-reported data and few studies examine interactions between job demands and job control.

Effort-reward imbalance

Introduction. The ERI model (ERI), proposed by Johannes Siegrist, focuses on the relation between the efforts individuals invest in their job and the rewards they receive in return. Efforts were initially divided into 'external efforts' (e.g. time pressure, heavy workload) and 'internal efforts' (a personal coping style in response to work demands) [92]. The concept of 'internal effort' was later revised and re-labelled as 'overcommitment' to work. Rewards consisted of salary, career opportunities, and recognition. The model posits that high levels of effort combined with inadequate rewards may cause adverse health outcomes, including cardiovascular disease, and that these effects may be amplified in individuals with high overcommitment. Thus, an important distinction between the ERI model and the JC model is the inclusion of a personality trait – overcommitment - as a stressor and a modifier of effects of environmental stressors.

Studies. We identified three follow-up studies providing six risk estimates on the association between perceived effort reward imbalance and risk of cardiovascular disease. These included a study of myocardial infarction among civil servants in London [93], a study from the IPD-Work Consortium compiling unpublished results on myocardial infarction from eleven European cohorts [22], and a Canadian study of ischemic heart disease among white-collar employees from 19 public and semi-public enterprises in the Quebec region of Canada [94]. In addition, one study exclusively addressed overcommitment [95].

Different self-administered questionnaires were used across studies to assess employees' perceptions of effort, reward, and overcommitment at baseline, varying in both content and response options (see Annex VIII). One study applied principal component analysis followed by confirmatory factor analysis to construct scales for *extrinsic effort* and *reward* based on available items that did not fully match the original ERI scale [96]. The derived scales showed acceptable internal consistency, with Cronbach's alpha values of 0.72 for effort (5 items) and 0.75 for reward (10 items). The IPD-Work Consortium study harmonized various partial ERI scales used in different cohorts by performing correlation analyses with data from studies using the original ERI scale [97]. The sensitivity and specificity of the effort-reward ratio, comparing partial to complete scales, were 59-93% and 85-99 %, respectively [98]. The Canadian study selected items from the original reward scale but substituted the efforts component with psychological demands questions from JCQ [94].

Effort–reward imbalance was quantified as the ratio of mean effort to mean reward scale scores, which was analysed either in quartiles (comparing the top three quartiles to the lowest), as a binary measure (ratio >1), or by contrasting the top 25% of the distribution with all others. Notably, none of the identified studies reported on the association between effort–reward imbalance and stroke.

Results. The three follow-up studies consistently reported associations between ERI and risk of ischemic heart disease (weighted average HR 1.18, 95% CI 1.03-1.35), but without exposure-response relationships in the main analysis in one study [93] (Figure 6-8, Table 2b, Annex VI-II). In this study, high efforts in combination with low rewards was not associated with increased risk of coronary heart disease in models with mutual adjustment for effort and reward (risk estimates not provided). One study reported increased risk only among men [94]. In two of the studies that separately reported effects of efforts, there were indications of increased risk associated with high effort and low reward levels.

None of the studies provided explicit data on the association between the effort–reward ratio and ischemic heart disease in models that simultaneously adjusted for the individual components (effort and reward). Consequently, it remains unclear whether the observed association is driven by one or both of the components or by their combination [93].

In a Taiwanese study of bus drivers, overcommitment—assessed independently of other ERI components—was associated with ischemic heart disease, but not with stroke [95] (see Annex VII). Overcommitment did not modify the effect of effort–reward imbalance in the IPD-Work Consortium study. In that study, the effect of effort–reward imbalance was independent of the effect of job strain [97].

Earlier reviews. Considering the popularity of the ERI hypothesis, it is surprising that only few studies have examined its association with cardiovascular diseases. We identified only one systematic review, which - based on two cohort studies and one case-control study - found that the evidence linking ERI to an increased risk of ischemic heart disease was limited [82]. Two of the studies included in that review were not eligible for our analysis, whereas two more recent studies included in our review were not covered in the earlier review [94, 97].

Consistency, bias, confounding and mediation. The three large and independent follow-up studies included in this review consistently suggest a prospective association between self-reported ERI and ischemic heart disease, despite variations in exposure metrics and outcomes. Risk estimates remained robust after adjustment for demographic and behavioural risk factors. However, important limitations persist across all three studies. These include crude exposure assessment performed at a single occasion at baseline, lack of comprehensive data on exposure-response relationships, modest risk elevations that may be susceptible to residual confounding, and no adjustment for the individual components of the ERI ratio (effort and reward) except in one study [93].

Summary of key points. Three cohort studies provide evidence for associations between perception of ERI and ischemic heart disease, but no studies addressed the risk of stroke. Several methodological limitations remain unresolved. Only two studies reported associations between the principal components of the model (efforts and rewards) and ischemic heart disease.

Job insecurity

Introduction. Job insecurity generally refers to the threat of losing one's job or uncertainty about continued employment. Although it may include concerns about the stability of future employment positions [99], most epidemiological studies focus on worries and perceived insecurity in the current job. Alternatively, employees in companies undergoing substantial downsizing or organisational restructuring may be considered exposed to job insecurity. This exposure extends over the period of organisational change, lasting until it is disclosed whether the employee will actually be dismissed or not. It has been hypothesized that employees who are still actively employed - whether perceived at the individual level or linked to organisational downsizing - may be a risk factor for cardiovascular disease. Several pathways have been proposed to explain this association. These include disturbed sleep, an increase of unhealthy behaviours, activation of the autonomic nervous system, endocrine stress reactions and psychological distress [48].

Studies. We identified six prospective follow-up studies that examined the risk of ischemic heart disease in relation to perceived job insecurity at baseline (Figure 9, Table 2c). In addition, two follow-up studies addressed cardiovascular disease mortality or morbidity in the context of workplace downsizing or organisational restructuring. Job insecurity was assessed using various self-administered baseline questions with dichotomous or graded response categories. In contrast, data on downsizing and organisational change were obtained from independent data sources such as employer electronic rosters or information provided by managers.

Results. The weighted average relative risk for ischemic heart disease across six studies with eight risk estimates was 1.16 (95% CI 1.05 -1.28). This estimate was not higher in three studies that specifically examined myocardial infarction (RR 1.09, 95% CI 0.95-1.25, Figure 9, Table 2c).

The IPD-Work Consortium study, which analysed unpublished individual participant data from 12 cohorts primarily based in Scandinavian countries, included 109,257 male and female employees. Among these, 1,346 cases of acute or recurrent myocardial infarction were identified through national health registries during 5 to 21 years of follow-up [16].

Most subcohorts assessed perceived job insecurity using single-item questions which either referred to insecurity in the current job or to a more general threat of being laid off. The average weighted, fully adjusted hazard ratio across the 12 cohorts was 1.05 (95% CI: 0.90–1.24). With the exception of one imprecise hazard ratio of 2.47 (95% CI: 0.99–6.16), based on a small, selected Danish study population, all estimates were either below 1 (six estimates) or slightly to moderately elevated (five estimates). All had wide confidence intervals that included 1. The adjusted risk estimates controlled for sex, age, and socio-economic position, as well as for a varying number of somatic (e.g. hypertension, diabetes) and behavioral (e.g. smoking, physical activity) risk factors for ischaemic heart disease. However, social network and other work-related psychosocial factors were not included in the analyses. Stratified analyses did not indicate any clear modifying effects of sex, age, national unemployment rates, welfare regime, or type of job insecurity.

The other five studies were two large US studies of nurses and women in health-related occupations [100, 101], the British Whitehall study of civil servants – which also was part of the IPD-Work Consortium study [102]) - and a smaller Danish study based on a random sample of citizens in Copenhagen (Figure 9) [103]. These studies used similar crude measures of perceived job insecurity as those applied in the IPD-Work Consortium study. All five studies reported higher risk estimates than the IPD-Work Consortium study, with HR's ranging from 1.19 to 2.50. The finding of the last study [103] is compatible with both a decreased and an increased risk. Only one study addressed the risk of stroke in relation to perceived job insecurity. This study found no increased risk (HR 0.94, 95% CI 0.63-1.40) [101].

Two studies used downsizing or organisational restructuring as an alternative approach to study job insecurity. Martikainen et al. conducted a large register-based follow-up study of Finnish men and women who remained employed during the severe economic recession in Finland in the 1990s [104]. This study examined mortality from ischaemic heart disease, among other specific causes. No excess mortality from ischaemic heart disease was found among those who kept their jobs, regardless of the level of downsizing in their workplace.

In contrast, Vahtera et al. reported different findings in another Finnish follow-up study [105]. They examined cardiovascular mortality among employees who remained in their jobs during a period of organisational downsizing. Cardiovascular mortality was found to be twice as high after major downsizing—defined as a reduction of staff by at least 18%—compared to workplaces without downsizing. The excess risk was particularly pronounced during the first years (HR 5.1, 95% CI: 1.4–19.3).

However, as pointed out by one of the external reviewers, this study did not fulfil the inclusion criteria because the outcome was cardiovascular mortality of all types.

Finally, a Danish prospective study of healthcare workers reported an excess risk of cardiovascular disease among employees who maintained their jobs during the year following organisational change in their work unit (HR 1.48, 95% CI 0.91-2,43) [46]. Information about organisational change was obtained from work unit managers prior to the start of follow-up. The elevated risk also applied to the subgroup of workers who explicitly experienced lay-off. This subgroup may serve as the best available independent proxy for job insecurity. However, the risk in this group did not differ significantly from that observed in the overall group experiencing organisational change.

Earlier reviews. We identified two systematic reviews addressing relations between job insecurity and cardiovascular disease. The first, by Virtanen et al., was a meta-analysis that combined results of four published cohort studies with data from 13 unpublished cohorts. It provided evidence of an association between job insecurity and incident coronary heart disease (fully adjusted RR 1.19, 95% CI 1.00-1.42, [16]). Part of this association may be attributable to socioeconomic and cardiovascular risk factors, which were more common among individuals reporting high levels of job insecurity. Our review includes a weighted average risk estimate from the 12 unpublished cohorts (excluding the Whitehall II study, which was published separately), along with all four published studies—except one that did not meet our eligibility criteria [106], see Annex V.

The second systematic review, by Anfossi et al., identified six studies addressing the risk of ischaemic heart disease [82]. Four of these studies are also included in our review [101-103, 107]. The remaining two studies were excluded from our review because they did not meet our inclusion criteria [106, 108], see Annex V for reasons. Conversely, Anfossi et al. did not include two studies that are part of our review [16, 100]. Studies using independent exposure assessments were not considered. The evidence synthesis by Anfossi et al. was based on a 'vote counting' approach, which considered the direction, size, and number of effects across studies, along with an assessment of likelihood of bias. The authors concluded that there was limited evidence supporting ‘harmfulness’ of job insecurity.

Consistency, bias, and confounding. The IPD Consortium study is considered highly informative due to several strengths: a large study population with broad transnational coverage across diverse demographic, occupational, and social contexts; strict and independent ascertainment of ischaemic heart disease; extensive adjustment for a wide range of confounders; and analyses stratified by subpopulation.

Although five other studies using similarly crude measures of job insecurity reported higher risk estimates [100-103], their findings remain compatible with those of the IPD Consortium.

A main limitation across all studies is the crude and heterogeneous assessment of job insecurity. In some studies, exposure was based on concerns about maintaining the current job. In others, it referred to more general fears of being laid-off. No data are available to evaluate whether these exposure measures accurately captured the intended constructs. Furthermore, exposure was measured only once at baseline, and none of the studies included exposure–response analyses.

Within the IPD-Work Consortium, results varied across subpopulations, and the risk of residual confounding by social and psychological factors remains. This may have biased the results in unpredictable directions. If medical and behavioral risk factors (e.g. smoking, hypertension) are mediators, adjusting for them may attenuate the observed associations. However, they might also act as confounders. Depressive mood, for example, is a known risk factor for ischaemic heart disease and may also be associated with more negative perceptions of job security. While this could inflate risk estimates, the crude exposure assessment limits the ability to detect true associations.

The studies on downsizing and organisational change provide independent insight into possible cardiovascular effects of job insecurity. In these studies, there is no risk of bias due to subjective appraisal of exposure, as exposure status is defined by characteristics of the company or the work-unit. However, findings are conflicting. Martikainen et al. did not find indications of increased ischemic heart disease mortality related to magnitude of staff reductions [104]. In contrast, the study by Vahtera et al. did lend support to the hypothesis of an association between job insecurity and cardiovascular outcomes, although the outcome included not only ischemic heart mortality but also mortality from other cardiovascular diseases. Further support for the association is provided by the Jensen et al. study addressing effects of organisational change [46]. Findings in a simulation of target trial addressing all-cause mortality in relation to shifting from precarious to standard employment was not eligible for this review but provide indirect evidence supporting the role of job insecurity [109]. On the other hand, a study based on the Whitehall II population explored potential mediators of the job insecurity–cardiovascular disease relationship. It found limited evidence that psychological distress -but not sleep disorders, allostatic load, or unhealthy behaviour - mediates the association [48]. Nonetheless, issues such as common method variance and reverse causation remain unresolved in that study.

Summary of key points. A slightly increased risk of ischemic heart disease associated with perception of job insecurity was corroborated by findings in five other cohort studies and partly supported by two of three studies on company downsizing or lay-offs. Limitations include crude and heterogeneous exposure assessment, lack of exposure-response data and residual confounding. Only one study addressed the risk of stroke.

Long weekly working hours

Introduction. A wide range of causal pathways has been proposed to explain how long weekly working hours may increase the risk of cardiovascular disease. These pathways are based on observed associations with a variety of risk factors known—or believed—to contribute to disease development [15]. Proposed mechanisms include excessive fatigue and exhaustion, limited opportunities for full recovery between work shifts, shorter sleep duration, and reduced leisure-time physical activity. Other contributing factors may be a competitive and high-strain personality type, as well as social isolation. All of these risk factors may increase with longer weekly working hours.

Studies. The association between weekly working hours and cardiovascular disease has been examined in nine prospective follow-up studies and one case–control study. Together, these provided 60 risk estimates related to working more than 40 hours per week. Estimates were stratified by specific outcomes, sex, occupational grade, or combinations of these variables (Table 2d, Figures 10–11).

In all studies, exposure was self-reported, except in the case–control study, where it was recalculated from individual salary records. Exposure was defined as the average number of hours worked per week, either for a single week or across several weeks leading up to baseline (in the follow-up studies), or prior to hospitalisation (in the case–control study).

In one study, exposure was based on reported overtime work [110]. In the remaining studies, it referred to the total number of weekly hours spent on salaried work, including extra jobs and work from home, but excluding commuting time. In most studies, the reference category was regular working hours of 35–40 hours per week.

Results. Working 40 to 55 hours per week was not associated with an increased risk of cardiovascular disease. The average weighted HR across studies was 1.02 (95% CI: 0.93–1.12) (Table 2d). Similarly, no increased risk was observed for ischaemic heart disease or stroke overall. However, two studies reported an elevated risk of haemorrhagic stroke, and one study found a higher risk of ischaemic heart disease among men with low physical fitness (Figure 10, Table 2d).

In contrast, working 55 hours or more per week was linked to a slightly increased risk of cardiovascular disease. This result was based on 20 risk estimates from eight studies and yielded a HR of 1.09 (95% CI 0.91–1.30). The elevated risk was primarily driven by a higher incidence of myocardial infarction (Figure 11, Table 2d).

Subgroup analyses indicated that the association between long working hours and cardiovascular disease was stronger in specific contexts. Higher risks were observed in studies conducted in non-Nordic countries, in occupational cohorts, and among blue-collar workers. Increased risk was also more apparent in studies with low response rates, small sample sizes, diagnoses not based on registries, and in those with longer follow-up periods (Tables 3c and 3d).

Earlier reviews. The weighted average risk estimates presented in this review are not conflicting with findings from five earlier systematic reviews regarding heart disease, but diverge with respect to stroke [15, 19, 23, 24, 111].

Regarding ischemic heart disease, a cumulative meta-analysis including 5 published cohort studies, and 20 unpublished cohorts found that working ≥55 h/w was associated with an increased risk. The reported relative risk, adjusted for age, sex, and socio-economic status (using 35–40 hours/week as the reference), was 1.13 (95% CI 1.02–1.26) [19]. A similar estimate was found in a subsequent systematic review conducted within the WHO/ILO Global Burden of Disease framework. That review, based on two published and 20 unpublished cohorts – largely the same studies as those included in Kivimäki et al. 2015 - reported a HR of 1.17 (95% CI 1.05–1.31) [24]. The authors classified the evidence for harmful cardiovascular effects at this exposure level as "sufficient" according to the Navigation Guide rating system.

Our review, based on five studies with nine risk estimates, found a comparable HR of 1.23 (95% CI 0.88–1.72) (Table 2d). The wider confidence intervals reflect substantial heterogeneity across studies. Three studies reported risk estimates close to one [24, 112, 113], while two studies reported approximately doubled risks [111, 114]. One of the latter was a case–control study, with potential recall bias due to partly self-reported working hours. Nevertheless, it was included because recent working hours were verified using company rosters.

In contrast to the two earlier meta-analyses, our review did not include unpublished cohorts identified via open-access platforms due to the use of self-reported outcome measures. Moreover, 10 unpublished European cohorts were represented in our meta-analysis by a single weighted random-effects estimate, as they were not considered independent and lacked the detailed documentation available for the original cohort publications.

With respect to stroke, findings from our review differ from earlier reviews. Virtanen and Kivimäki, in an update of a prior review, reported an increased risk of stroke among employees working more than 55 hours per week. This result was based on 16 predominantly unpublished studies and yielded a meta-analytic risk estimate of 1.21 (95% CI 1.01–1.45) [115]. These results were supported by the most recent systematic review from the WHO/ILO framework, which reported a HR of 1.35 (95% CI: 1.13–1.61) based on seven studies [23]. Using the Navigation Guide, the evidence was again rated as sufficient for "harmfulness."

In contrast, our review found no increased risk of stroke associated with working 55 or more hours per week. Based on five studies with 11 risk estimates, the average hazard ratio was 1.01 (95% CI: 0.87–1.16). Notably, one of the studies included in the Descatha review did not meet our inclusion criteria, as it was a cross-sectional study relying on self-reported diagnoses [116]. Furthermore, several cohort studies retrieved via open-access sources were excluded from our analysis due to the use of self-reported outcome measures. Finally, our review included several robust and highly informative studies that were not part of the Descatha review [112, 113, 117].

Internal consistency. Among the studies included in this review, several inconsistencies are worth noting. The Whitehall II study of civil servants in London and a Japanese hospital-based case–control study both found an increased risk of ischaemic heart disease among employees working long hours [110, 114]. In contrast, a reanalysis of unpublished studies conducted by the IPD-work Consortium—limited to those meeting the inclusion criteria for the present review—reported an increased risk for stroke, but not for ischaemic heart disease [19]. Furthermore, three other large follow-up studies provided no robust evidence of increased risk for either outcome [112, 117, 118].

Cardiovascular disease exhibits a strong socioeconomic gradient. However, findings on the association between long working hours and cardiovascular disease, when stratified by occupational grade, are inconsistent. For example, the Whitehall II study - comprising civil servants equivalent to white-collar workers - reported an increased risk of ischaemic heart disease associated with long working hours [110]. In contrast, a large census-based study from Ireland found increased mortality from ischaemic heart disease only among male workers in routine occupations. No elevated risk was observed among managers, professionals, employees in intermediate occupations, or self-employed individuals [113]. Similarly, a Danish nationwide follow-up study reported only indications of increased ischaemic heart disease risk linked to long working hours, and this was limited to individuals in lower socioeconomic groups [117].

Confounding and bias. Observational studies examining the cardiovascular effects of long working hours are prone to various sources of bias and confounding, which may distort risk estimates in either direction. For instance, working fewer than standard hours may, in some populations, be associated with pre-existing cardiovascular morbidity [114]. If such individuals are included in the reference group, this may bias risk estimates toward the null.

Conversely, residual confounding from unmeasured cardiovascular risk factors is an issue, as many studies did not fully account for these. Although some adjusted for medical and behavioural risk factors, none controlled for key determinants of cardiovascular disease such as family history, social isolation, or early life adversity [91].

Moreover, any potential effect of long working hours is likely modified by other aspects of the working environment. Co-exposures to physically or mentally strenuous working conditions and adverse psychosocial factors—such as high psychological demands, low job control, poor organisational justice, or limited social support—may influence outcomes and interact with working hours to amplify cardiovascular risk.

Summary of Key Points. Eight follow-up studies and one case–control study found no evidence of an increased risk of ischaemic heart disease or stroke associated with working 40–55 hours per week. In contrast, findings for working 55 hours or more per week were inconsistent. Any potential effects of long working hours on cardiovascular health are likely dependent on concurrent exposure to physically or mentally demanding working conditions.

Other exposures

(Downsizing (two studies) and organisational change (one study) is described in relation to job insecurity. Author comments to the individual studies are in this section enclosed by square brackets)

Workplace resources. Xu et al. (2022) investigated prospective associations between workplace resources and risk of cardiovascular disease in three large Swedish and Danish cohorts, comprising a total of 135,669 employees [60]. The study distinguished between horizontal workplace resources (e.g. culture of collaboration, support from colleagues) and vertical workplace resources (e.g. leadership quality, procedural justice). Compared to employees with low levels of both horizontal and vertical resources (13% of the sample), those reporting high levels in both dimensions (28%) had reduced risks of incident myocardial infarction (179 cases, HR 0.88, 95% CI 0.70–1.09), ischaemic stroke (172 cases, HR 0.91, 95% CI

0.72–1.15), and notably, haemorrhagic stroke (28 cases, HR 0.58, 95% CI 0.35–0.96). Risk estimates were adjusted for age, sex, country of birth, education, marital status, pre-existing comorbidity, prior mental disorders, and type of employment contract. However, trend tests were not reported.

[The study extends earlier findings in studies addressing risk of cardiovascular disease in relation to various measures of quality of management, procedural and relational justice, and social support at work [81, 119-121]. In particular, a high level of perceived relational justice at work was associated with a reduced risk of coronary heart disease in the Whitehall II study, independently of other psychosocial work exposures (HR 0.69, 95% CI 0.49–0.98) [119]. However, in that study there were no indications of exposure-response relationships and no fully adjusted analyses [119]

The clustering of vertical and horizontal dimensions of workplace resources represents a new promising approach. Despite a large study population and extensive analysis, the use of self-reported data and lacking data on exposure-response associations are considered a limitation for causal inference. Thus, there is a need for studies addressing the same type of exposures by objective measures of workplace resources or intervention studies on effects of organisational changes].

Bullying and violence. Xu et al. (2019) examined prospective associations between perceived workplace bullying and violence and the risk of cardiovascular disease in three Swedish and one Danish cohort, with an average follow-up period of 12 years using national health and mortality registers [59]. Cardiovascular disease was defined as either coronary heart disease or cerebrovascular disease. Across the four cohorts, the fully adjusted risk estimate was elevated following exposure to workplace bullying (HR 1.59, 95% CI 1.28–1.98), and to a lesser extent after reported exposure to workplace violence (HR 1.25, 95% CI 1.12–1.40). There was also some indication of a dose–response relationship, with higher disease risk observed among those reporting more frequent exposure. Risk was increased for both coronary heart disease and cerebrovascular disease.

[This study represents the first large, population-based prospective investigation of the association between perceived workplace bullying and violence and cardiovascular disease. The subjective nature of exposure assessment may introduce reporting bias. Furthermore, despite the use of objectively verified health outcomes, residual confounding related to personality traits, behavioural factors, and other cardiovascular risk factors linked to self-reported exposure cannot be ruled out with confidence].

Workplace sexual harassment. KC et al. (2024) examined prospective associations between perceived workplace sexual harassment during the past 12 months (4.8%) and risk of fatal and non-fatal cardiometabolic disease in a Swedish cohort of 88,904 employees [122]. Risk estimates were adjusted for a wide range of socio-demographic, work-related psychosocial, and physical exposures. The fully adjusted risk estimates were elevated for myocardial infarction (HR 1.26, 95% CI.92-1.71) and marginally elevated for stroke (HR 1.08, 95% CI 0.77-1.51), and essentially similar to unadjusted risk estimates.

[This is the first large prospective study investigating the association of workplace sexual harassment and cardiovascular disease. The findings seem consistent with studies addressing sexual harassment and violence in general [123] and myocardial infarction was slightly more common in employees reporting frequent versus occasional harassment. However, residual confounding and bias cannot be out ruled with confidence, given the subjective nature of the exposure assessment].

Predictability on the job. Väänänen et al. (2008) investigated the association between components of job control—specifically decision authority, skill discretion, and predictability on the job—and the risk of fatal and non-fatal acute myocardial infarction in a cohort of 7,663 industrial employees from a large Finnish forest company (the Still Working Study) [124]. Predictability on the job was defined by clarity of work goals and opportunity to anticipate changes and problems at one's work. After adjusting for demographic characteristics, psychological distress, pre-existing medical conditions, lifestyle risk factors, and socioeconomic status, predictability - but not decision authority or skill discretion - was significantly associated with increased risk of acute myocardial infarction (HR 1.13, 95% CI 1.01–1.26).

[This study contributes to earlier evidence by splitting the job control dimension into distinct components, suggesting that the ability to foresee changes in working conditions may be an important psychosocial factor in cardiovascular risk. A limitation, however, is the absence of mutual adjustment for the other job control components in the analysis].

Job satisfaction and dissatisfaction. Netterstrøm et al. 2010 examined associations between job dissatisfaction and risk of hospitalisation because of ischemic heart disease in a population-based sample of citizens in Copenhagen [125]. Job dissatisfaction was measured by two questions ('thought of seeking another job?', yes/no and 'Are you satisfied with your work?', yes/no). The fully adjusted risk was elevated in women (OR 3.0, 95% CI 1.2-7.6), but not in men (OR 0.9, 95% CI 0.3-3.3). This result was reported along with a range of other exposures related to the DC model and was not analysed further. An earlier study examined change in job satisfaction, and its association with cardiovascular mortality using longitudinal data from a Scottish cohort of men and women [126]. As half of the cohort provided a second round of data 4-7 years after baseline, it became feasible to examine effects of change in job satisfaction. Change in job dissatisfaction was not associated with cardiovascular mortality in men or women. This study included all types of cardiovascular diseases (ICD-9 codes 390-459) and is not directly comparable to the study of Netterstrøm et al 2010. Another early population-based follow-up study examined marital, parental and job characteristics with respect to risk of ischemic heart disease and stroke. High work-satisfaction was not related to either outcome in sex-stratified analyses [127].

[Few studies on the effect of job dissatisfaction did not provide consistent evidence of associations between perceived workplace satisfaction and cardiovascular disease].

Work pressure/speed. Allesøe et al. (2009) [128] investigated the association between perceived work pressure and influence at work and the risk of ischaemic heart disease in a large nationwide cohort of Danish nurses. The study was characterised by a high participation rate at baseline and complete follow-up via the Danish National Hospital Register. Work pressure was measured using a single item with the following response categories: "Much too low," "A little too low," "Appropriate," "A little too high," and "Much too high." Influence at work was assessed with the question: "Normally, how great is your influence on the organisation of your daily work?" with response options: "Major influence," "Certain influence," and "Minor or no influence."

Among nurses under the age of 51 at baseline, those reporting that their work pressure was "much too high" had an increased risk of ischaemic heart disease compared to those reporting "appropriate" levels of work pressure (HR 1.94, 95% CI 1.25–3.01), after adjusting for a broad range of cardiovascular risk factors. In contrast, influence at work was not associated with the outcome.

[The strengths of the study include the large and relatively homogeneous population, high response rate, complete follow-up, and adjustment for several relevant covariates. A limitation is the broad definition of the ischaemic heart disease outcome, which included angina pectoris—a diagnosis not extensively validated and often managed outside of hospital settings. This could result in overestimation of risk if perceived high work pressure increases the likelihood of hospitalisation for this condition. Nevertheless, this limitation is likely less relevant in recent years and in certain countries. For instance, in Sweden, hospitalisations for angina pectoris among women aged 35–74 declined by 90% between 1998 and 2022, and the condition has become distinctly uncommon. Over the same period, coronary heart disease mortality decreased by 75%].

Psychological demands and resources. Lynch et al. 1997 examined how socioeconomic class defined by income level modified the association between the combination of high psychological demands and low resources at work on one hand and myocardial infarction on the other hand. The study included a population-based sample of men in Finland [129]. Psychological demands were broadly defined and included issues such as problems with supervisors and deadlines, while the resource variable resembles the control variable in the DCS model. Authors concluded that effects are modified by income and by and largely mediated through known risk factors.

DISCUSSION OF GENERAL ISSUES

In this systematic review, we synthesized the evidence on associations between psychosocial workplace exposures and cardiovascular disease using predefined, rigorous criteria for study design, exposure and outcome ascertainment, and statistical analysis to identify the most informative studies. A total of 59 epidemiological studies published between 1977 and 2024 were included.

Based on 315 estimates of relative risk, we found indications of increased risk of ischaemic heart disease or stroke associated with job strain, effort–reward imbalance, job insecurity, and weekly working hours exceeding 55. Additional studies examined cardiovascular risk in relation to other exposures, including horizontal and vertical workplace resources, workplace bullying and violence, sexual harassment, job predictability, and job dissatisfaction. While these studies suggested some associations, they were too few in number to support firm conclusions regarding causality.

We only included studies that provided risk estimates adjusted for sex, age and some measure of socio-economic position – by analysis, stratification or design. These factors are all considered strong determinants of cardiovascular disease: increased risk by male sex, higher age and lower socio-economic position. The direction of bias if these factors were not accounted for may be in either direction depending on the study population and the variable distribution across groups that are compared.

Several design, analytical, and measurement issues may have attenuated the reported associations. These include limited exposure contrast, as no studies focused on populations with a priori documented high exposure levels. Moreover, except for long weekly working hours, exposures were often grouped into broad categories, potentially obscuring effects among smaller groups with more extreme exposure levels. For example, exposures measured on scales derived from questionnaire items—such as job demands and job control—were commonly categorized into tertiles or quartiles. However, due to the highly skewed distribution of these exposures, such groupings may reflect only minimal differences in absolute scores.

Second, most studies relied on a single self-reported exposure assessment at the start of follow-up, often spanning several years, without accounting for changes in exposure or estimating the effects of cumulative exposure.

Third, adjustment for behavioral risk factors (e.g., smoking, sedentary lifestyle) and medical conditions (e.g., hypertension, hypercholesterolemia) may have biased risk estimates toward the null if these factors are on the causal pathway from psychosocial stressors to cardiovascular disease. In many studies, such adjustments did indeed attenuate risk estimates. Similarly, several studies adjusted risk estimates for distress and depression which also might result in deflationary bias to the extent these factors are mediators of observed effects. However, because these factors were typically measured only once at baseline, concurrently with exposure, they could also introduce inflationary bias if not appropriately adjusted for if they occur temporally prior to the onset of exposure.

Finally, other factors that may obscure or attenuate true causal associations include healthy worker selection, particularly in studies enrolling participants later in life where more resilient "survivors" of adverse psychosocial conditions may be overrepresented [130], and poor validity of exposure measures. For instance, job demands and control may be interpreted differently across social groups, affecting comparability and precision of exposure assessment [78].

Although numerous factors may obscure causal links between psychosocial workplace exposures and cardiovascular disease, there are also important issues that could lead to falsely elevated risk estimates [33]. First, most studies relied on self-reported exposure data. Despite prospective designs with independent outcome assessment, it has long been acknowledged—including by Robert Karasek as early as 1982—that individuals who assess their work environment less favourably may also experience poorer health and be more likely to seek medical care, potentially increasing the likelihood of disease detection [131]. This issue can be circumvented in studies of cause-specific mortality, in which risk estimates—when reported—have generally been lower than corresponding estimates based on disease incidence for exposures such as job strain, iso-strain, and long working hours. Furthermore, studies using independent exposure assessments (e.g. job exposure matrices) did not convincingly corroborate findings obtained in the majority of studies based upon self-reported exposure assessment.

Second, residual confounding is a concern, particularly given that any true elevation in risk is likely small or modest. Socioeconomic factors—especially education and occupational class—are strongly associated with both cardiovascular outcomes and workplace exposures such as job demands, decision authority, and skill discretion [34-37, 132, 133]. We only included studies that to some extent accounted for socio-economic position, but this does not imply that adjustment was sufficient. For instance, job strain remained a significant predictor when adjusted for income, but not when education was also included in the model [70].

Third, several studies adjusted risk estimates for a range of other less robust antecedents of cardiovascular disease such as ethnicity, family history or personality thus limiting likely inflationary bias by these factors. However, few studies accounted for childhood adversity [69, 134], limited social network or loneliness [135, 136] and most studies did not adequately control for other workplace exposures that are closely related to the psychosocial exposures under investigation—particularly the component variables of composite measures like job strain and effort–reward imbalance.

Finally, in addition to concerns about biased exposure data and residual confounding, the potential for publication bias and selective reporting in large studies examining numerous exposures and outcomes further complicates the synthesis and interpretation of the evidence.

Summing up, there are several sources of bias that likely may inflate as well as attenuate risk estimates. Unfortunately, it is not possible reliably to quantify these biases and hereby predict the net effect. Explanations for the strong heterogeneity of study results - some reporting effects and others not – remain unresolved.

We included mortality studies if the cause of death was ischemic heart disease and/or stroke. Studies including other cardiovascular outcomes such as pulmonary embolism or hypertensive disease were excluded. Since ischemic heart disease and stroke are leading causes of cardiovascular mortality, we may have missed important information. In all, five cardiovascular mortality studies were excluded by use of the strict inclusion criteria. These studies addressed job strain and effort reward imbalance [137], organisational justice [138], downsizing [105], job dissatisfaction [133] and job control [139], respectively. Although the studies are high quality epidemiological studies, they address different psychosocial exposures and are therefore not critical for the final evaluation of causal inference.

The studies included in this review display substantial heterogeneity in terms of geography, population demographics, sampling procedures, exposure and outcome measures, and analytical approaches. These differences can violate assumptions of homogeneity for meta-analytic interpretation. As a result, the meta-analytic risk estimates and confidence intervals do not necessarily correspond to parameters that reflect real-world populations. These estimates should not be interpreted literally. Rather, in the absence of more suitable alternatives, they offer an approximate indication of the direction and magnitude of the effect. Their interpretation must also take into account the influence of bias and confounding.

Various pathophysiological mechanisms have been suggested to explain how psychosocial factors may influence cardiovascular disease [10, 140]. One pathway involves activation of the autonomic nervous system, leading to increased catecholamine release. This can cause acute circulatory effects such as elevated blood pressure and increased heart rate, as well as initiate an inflammatory response that may contribute to vascular damage and atherosclerosis over time. Concurrently, activation of the hypothalamus-pituitary-adrenal axis increases cortisol secretion, which, among other effects, may promote blood clot formation through effects on metabolism, platelets and coagulation factors. The former mechanism—accelerated atherosclerosis—is typically associated with long latency, while the latter—effects on coagulation—may act as a short-term trigger. However, direct evidence linking activation of the autonomic nervous system and diurnal cortisol secretion to cardiovascular disease is limited [141].

Some support for a causal link between psychosocial workplace exposures and ischemic heart disease or stroke comes from evidence suggesting that factors such as job strain and effort–reward imbalance leads to increases in established cardiovascular risk factors – such as hypertension, smoking, obesity, physical inactivity, metabolic syndrome, and various biomarkers such as blood lipids and heart rate variability [142-145]. Hereby, work stress may indirectly contribute to cardiovascular disease by influencing intermediary health behaviours.

It has also been argued that workplace stressors may trigger acute cardiovascular events—such as myocardial infarction or stroke—in individuals with advanced atherosclerosis. This could occur through mechanisms including increased sympathetic activation, elevated blood pressure, a lowered arrhythmic threshold, and stimulation of inflammatory and procoagulant responses [10].

In summary, workplace stressors may contribute to cardiovascular disease through both long-term effects and short-term triggering mechanisms. Although there is no shortage of plausible biological pathways, actual demonstrations that one or more of these factors mediate the relationship between workplace stressors and cardiovascular disease remain limited.

Potential additive or even interactive effects of co-exposure to several types of workplace stressors is important, in particular when exposures are not conceptually overlapping as for instance long working hours in combination with high job demands and when at least one of considered stressors is likely to have causal cardiovascular effects. Although few studies address effects of multiple exposures (e.g. [146]), there is a notable lack of such research.

Even if it is assumed that certain psychosocial workplace stressors—such as job strain—are causal risk factors for ischemic heart disease, the average relative risk remains well below a twofold increase. This implies that, on average, the disease in an exposed employee is more likely to result from other, potentially unmeasured factors, including alternative work-related exposures.

While a crude probability assessment can be refined by considering the presence or absence of various known risk factors, data on exposure–response relationships—such as the intensity and duration of exposure—and on the timing of disease onset relative to exposure (i.e., long-term effects versus triggering events) are too limited to support further evaluation of whether a work-related disorder is present in an individual case.

The JC work stress model has dominated research in occupational psychosocial epidemiology for decades. One likely reason is the tendency in applied epidemiology to adhere to established methods, which facilitates broader acceptance and comparability across studies. However, entirely new approaches are emerging that have a strong focus on organisational aspects of work. These may prove valuable for research because of options for objective exposure metrics and for occupational practise if specific modifiable harmful organisational characteristics can be identified [147, 148]. Moreover, few observational studies on workplace stressors and cardiovascular disease apply study designs that emulate the classic randomized controlled study. Studies on health effects of major downsizing of company staffs during period with economic crises may be considered a natural experiment of effects of downsizing [104, 105]. A range of other design options are available but often not easily applied in psychosocial epidemiology [149].

CONCLUSIVE EVIDENCE SYNTHESIS

Demand-control-support model. A large body of high-quality cohort studies address links between job strain and risk of ischemic heart disease and stroke. Given the unresolved inconsistencies across many studies, the small magnitude of risk estimates when elevated, the likely presence of bias and confounding with unpredictable net effects, and the absence of demonstrated exposure–response relationships, the evidence that job strain and isostrain cause ischemic heart disease or stroke remains limited. Nonetheless, the available data do not rule out small effects of job strain and isostrain.

Effort-reward imbalance. The evidence supporting a causal link between perceived ERI and risk of ischemic heart disease is limited. There are few independent studies, and the few that exist are limited by crude exposure assessment, lack of comprehensive data on exposure-response and outcome specificity and small risk elevations susceptible to residual confounding. No or too few eligible studies were available to permit separate evaluation of effects of efforts, rewards and overcommitment or presence or absence of a causal relationship between perceived ERI and risk of stroke.

Job insecurity. The evidence supporting a causal link between job insecurity and risk of ischemic heart disease is limited. There are few independent studies which are limited by crude exposure assessment, lack of comprehensive data on exposure-response, likely residual confounding and unresolved inconsistencies in studies using independent data on job insecurity. The available data are insufficient to permit evaluation regarding the presence or absence of a causal relationship between perceived job insecurity and risk of stroke (only one study only addressing women).

Long working hours. The evidence supporting a causal link between working long weekly hours and risk of ischemic heart disease or stroke is limited. Several studies suggest a modest increased risk of both ischemic heart disease and stroke related to working more than 55 hours. However, inconsistencies across studies, residual confounding, and lack of data on occupational co-exposures limit causal inference.

Other work-related psychosocial exposures (workplace resources, bullying and violence, sexual harassment, predictability, job dissatisfaction and work pressure/speed). The epidemiological evidence is sparse and does not allow for causal inference.

Summary of key issues in relation to interpretation of causality of associations between psychosocial exposures and cardiovascular outcomes is provided in the following table.

+ = yes; (+) = partly, 0 = no; - = undetermined, blank = not appropriate

	Studies (N)	Distribution of risk estimates (variance weighted average across studies) (N)				No consistency across studies	Potential confounding	No independent exposure assessment	No exposure-response	Publication bias
		HR < 1.0	1.0-1.25	> 1.25	P < 0.05					
Job strain	26	5	12	9	10	+	+	(+)	+	+
Isostrain	4	1	2	1	2	0	+	+	+	
Demands	19	8	8	3	8	+	+	+	(+)	
Control	24	7	12	5	8	+	+	+	(+)	
Support	9	1	7	1	4	+	+	+	+	
Effort-reward imbalance	3	0	1	2	2	0	+	+	+	
Efforts	2									
Rewards	2									
Commitment	2									
Job insecurity	6	0	4	2	2	-	-	(+)	+	
Long weekly working hours 40-55	8	2	6	0	0	-	-	-	+	
Long weekly working hours 55+	8	4	2	3	2	+	+	(+)	(+)	
Low horizontal and vertical workplace resources	1	0	1	0	1					
Workplace-related bullying and violence	1	0	0	1	1					
Workplace-related sexual harassment	1	0	1	0	0					
Job-related unpredictability	1	0	1	0	1					
Job dissatisfaction	3	1	1	1	0	+	+	+	+	
Work pressure/speed	1	0	0	1	1					

CLASSIFICATION OF THE EVIDENCE

The evidence synthesis was summarized according to classification requested by the Danish Work Environment Fund (for definitions see next page). A key issue is whether it 'not likely' (++) or 'not unlikely (+)' that a given exposure-outcome association can be explained by chance, bias or confounding. Because of the availability of many large high-quality epidemiological studies, chance findings were not considered an issue. The main reasons for classifying the evidence as 'limited (+)' rather than 'likely (++)' are unresolved inconsistencies across studies, risk estimates of small or modest magnitude, likely risk of bias and confounding, with a net effect in an unpredictable direction, lack of comprehensive data on exposure-response relationships and limited evidence of biological mechanisms that mediate the associations.

Classification of evidence for causality according to the criteria used by the Danish Work Environment Fund.

	Ischemic heart disease	Stroke
High job demands	0	0
Low job control	(+)[1]	0
Low social support	+	0
Job strain	+	+
Isostrain	+	0
High efforts	0	0
Low rewards	0	0
High commitment	0	0
Effort-reward imbalance	+	0
Job insecurity	+	0
Working hours 40-55 hours per week	0	0
Working hours 55+ hours per week	+	+
Low horizontal and vertical workplace resources	0	0
Workplace-related bullying and violence	0	0
Workplace-related sexual harassment	0	0
Job-related unpredictability	0	0
Job dissatisfaction	0	0
Work pressure/speed	0	0

+++ = strong evidence for causality; ++ = likely evidence for causality; + = limited evidence for causality; 0 = insufficient evidence for causality; - = good evidence for lack of causality.

[1] (+) There is limited evidence for causality. Risk estimates in most studies are close to 1 with confidence intervals including 1.

Definition of evidence for causality by Work environment Fund

Strong evidence for causality (+++):	**A causal relationship is very likely.** A positive relationship between exposure to a risk factor and outcome has been observed in several epidemiological studies. It can be ruled out with reasonable certainty that this relationship is explained by chance, bias or confounding.
Likely evidence for causality (++):	**A causal relationship is likely.** A positive relationship between exposure to a risk factor and outcome has been observed in several epidemiological studies. It cannot be ruled out with reasonable certainty that this relationship can be explained by chance, bias or confounding, although this is not a particularly likely explanation.
Limited evidence for causality (+):	A causal relationship is possible. A positive relationship between exposure to a risk factor and outcome has been observed in several epidemiological studies. It is not unlikely that this relationship can be explained by chance, bias or confounding.
Insufficient evidence for causality (0):	The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a causal relationship.
Good evidence for lack of causality (-):	Several studies of sufficient quality, consistency, and statistical power suggest that the specific risk factor is not causally related to the specific outcome.

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TABLES: OVERVIEW

Table 1a. Characteristics of studies (N=59) addressing psychosocial workplace exposures and ischemic heart disease or stroke.

	Studies (N)	Studies by outcome (N)		
		Ischemic heart disease	Stroke	Cardiovascular disease[1]
All	59	48	20	4
Countries				
Nordic countries	29	22	10	4
UK and Ireland	6	6	1	0
Europe, other or several countries	9	7	4	0
USA and Canada	11	11	2	0
Korea, Japan, and Taiwan	4	2	3	0
Populations				
Population-based, national samples	13	10	7	0
Populations-based, other samples	14	10	4	2
Occupational samples	16	14	5	2
White collar workers	10	9	1	0
Blue collar workers	4	3	3	0
Case-control studies	2	2	0	0
Exposure ascertainment				
Self-administered questionnaire or interview	44	36	15	3
Job exposure matrix, survey based	8	7	3	0
Job exposure matrix, expert based	2	2	1	0
Company rosters, registers, managers	5	3	1	1
Outcome ascertainment				
Hospital diagnosis or death register	41	32	15	4
Medically verified self-report	10	9	3	0
Clinical examination	5	5	0	0
Other	3	2	2	0
Outcome specificity[2]				
CVD unspecified	3	1	1	3
CVD mortality	1	0	0	1
Myocardial infarction	18	18	5	1
IHD unspecified	26	26	6	1
IHD mortality	7	7	4	0

	Ischemic stroke	10	5	10	1
	Haemorrhagic stroke	7	2	7	1
	Stroke unspecified	8	4	8	1
	Stroke mortality	5	4	5	0
Gender distributions					
	0 - 25% women	17	16	5	0
	> 25-50% women	29	24	10	3
	> 50% women	10	7	3	1
	Missing	3	1	2	0
	Only men	15	14	5	0
	Only women	8	6	3	0
Primary participation of eligible					
	<75%	19	13	8	2
	75 - <100%	15	14	5	0
	100%	8	7	2	0
	Missing	17	14	5	2
Follow-up, entry year					
	Before 1990	21	20	6	0
	1990 - < 2000	27	19	9	2
	2000-	11	9	5	2
Follow-up, duration, years[3]					
	1-5	7	5	1	1
	6-10	19	15	7	2
	> 10	27	23	11	1
	Missing	6	5	1	0
Number of cases					
	< 100	5	4	1	1
	100- < 500	21	17	4	1
	500- <1000	14	11	4	1
	1000+	19	16	11	1

[1] Ischemic heart disease and stroke combined
[2] Studies do not sum up to 59 as one study may contribute to several outcomes
[3] Not including two case-control studies

Table 1b. Psychosocial exposures in studies (N=59) addressing ischemic heart disease or stroke.

	All		Ischemic heart disease		Stroke		Cardiovascular disease	
Exposure	Studies	Risk estimates	Studies	Risk estimates	Studies	Risk estimates	Studies	Risk estimates
Demands	19	50	16	35	4	9	3	6
Control	24	58	20	38	6	15	3	5
Social support	9	23	8	14	3	7	1	2
Job strain	26	49	21	32	7	13	2	4
Isostrain	4	9	2	3	2	0	3	6
Effort	2	3	2	3	0	0	0	0
Reward	2	3	2	3	0	0	0	0
Commitment	2	3	2	2	1	1	0	0
Effort reward imbalance	3	6	3	6	0	0	0	0
Insecurity	6	9	6	8	1	1	0	0
Long working hours	10	60	7	28	5	32	0	0
Other	12	42	11	24	4	11	2	7
Repeated exposure assessments	7	36	6	20	0	0	2	16
Exposure response data	29	170	25	119	9	48	1	3
Cumulative exposure assessment	2	21	2	11	0	0	1	10
Analysis of interaction between demands and control	4	23	3	15	0	0	1	8

Table 1c. Covariates in studies (N=59) addressing psychosocial workplace exposures and ischemic heart disease or stroke.

		All	Ischemic heart disease	Stroke	Cardiovascular disease
All		59	48	20	4
Socioeconomic variables					
	Education	37	31	13	3
	Income	18	17	5	1
	Occupational class or grade	42	35	14	3
	Marital status	25	22	8	3
Potential confounders					
	Ethnicity or race	16	15	5	1
	Family history of cardiovascular disease	8	8	2	0
	Personality	4	4	0	0
	Comorbidity	10	10	3	1
	Childhood adversity	5	4	1	1
	Social network	13	11	3	3
	Residence	11	10	2	1
	Calendar year	11	9	4	0
	Other work-related exposures	24	20	8	2
Potential modifiers and/or confounders					
	Physiological risk factors (hypertension, hyperlipidaemia, diabetes)	34	29	7	2
	Behavioural risk factors (smoking, alcohol, physical activity)	39	34	8	2
	Distress and depression	12	10	3	3

Table 2a. Meta-analytic random effect risk estimates (RR)[1] for **DEMAND-CONTROL-SUPPORT VARIABLES** and cardiovascular disease outcomes. Within-study stratified risk estimates were pooled (one risk estimate per study). If risk was given by exposure level, only the highest level was used.

Exposure	Outcome	Studies[2] (N)	Estimates (N)	RR	95% CI
High job strain					
	CVD overall	26	49	1.13	1.06-1.21
	IHD or stroke unspecified	2	4	1.10	0.64-1.89
	IHD overall	21	32	1.14	1.06-1.23
	Myocardial infarction	11	14	1.08	1.00-1.15
	IHD unspecified	9	15	1.26	1.09-1.47
	IHD mortality	2	3	1.13	0.98-1.31
	Stroke overall	7	13	1.19	1.03-1.37
	Ischemic stroke	4	4	1.20	1.05-1.38
	Haemorrhagic stroke	2	2	0.97	0.74-1.27
	Stroke unspecified	3	7	1.41	0.94-2.11
	Stroke mortality	0	0	-	-
High job demands					
	CVD overall (IHD or stroke)	19	35	1.02	0.96-1.09
	IHD or stroke unspecified	3	5	0.99	0.79-1.25
	IHD overall	16	24	1.03	0.96-1.11
	Myocardial infarction	7	10	1.06	0.94-1.18
	IHD unspecified	6	10	0.97	0.97-1.03
	IHD mortality	3	4	1.01	0.87-1.18
	Stroke overall	4	6	1.16	0.90-1.51
	Ischemic stroke	2	2	1.08	0.88-1.33
	haemorrhagic stroke	1	1	0.90	0.41-1.96
	Stroke unspecified	2	3	1.40	0.77-2.52
	Stroke mortality	0	0	-	-
Low job control					
	CVD overall (IHD or stroke)	24	47	1.07	1.03-1.12
	IHD or stroke unspecified	3	5	1.21	1.01-1.44
	IHD overall	20	30	1.10	1.03-1.18
	Myocardial infarction	9	13	1.08	1.02-1.14
	IHD unspecified	8	13	1.02	0.88-1.18
	IHD mortality	3	4	1.12	1.05-1.19
	Stroke overall	6	12	1.03	0.99-1.08
	Ischemic stroke	2	2	1.11	0.87-1.42
	haemorrhagic stroke	1	1	1.10	0.50-2.41
	Stroke unspecified	3	5	0.97	0.88-1.07
	Stroke mortality	1	4	1.05	1.00-1.09

Exposure	Outcome	Studies[2] (N)	Estimates (N)	RR	95% CI
Low social support					
	CVD overall	9	18	1.10	1.00-1.21
	IHD or stroke unspecified	1	2	1.14	0.92-1.41
	IHD overall	8	11	1.10	0.99-1.24
	Myocardial infarction	3	3	1.06	0.94-1.19
	IHD unspecified	4	6	1.25	0.85-1.85
	IHD mortality	1	2	1.21	0.99-1.48
	Stroke overall	3	5	1.00	0.87-1.15
	Ischemic stroke	2	2	0.92	0.76-1.10
	Haemorrhagic stroke	1	1	1.10	0.47-2.56
	Stroke unspecified	1	2	1.11	0.90-1.39
	Stroke mortality	0	0	-	-
High isostrain					
	CVD overall	4	9	1.21	1.06-1.38
	IHD or stroke unspecified	3	6	1.11	0.95-1.30
	IHD overall	2	3	1.46	1.12-1.91
	Myocardial infarction	0	0	-	-
	IHD unspecified	1	1	1.92	1.05-3.52
	IHD mortality	1	2	1.14	0.96-1.35
	Stroke overall	0	0	-	-
	Ischemic stroke	0	0	-	-
	Haemorrhagic stroke	0	0	-	-
	Stroke unspecified	0	0	-	-
	Stroke mortality	0	0	-	-

[1] Meta-analytic risk estimates are based on the fully adjusted risk estimates, minimally adjusted for sex, age and some measure of socio-economic position.

[2] The number of studies does not add up to total numbers because some studies contributed to more than one outcome.

Table 2b. Meta-analytic random effect risk estimates (RR)[1] for **EFFORT-REWARD IMBALANCE VARIABLES** and cardiovascular disease outcomes. Within-study stratified risk estimates were pooled (one risk estimate per study). If risk was given by exposure level, only the highest level was used.

Exposure	Outcome	Studies (N)[2]	Estimates (N)	RR	95% CI
High effort-reward imbalance					
	CVD overall	3	4	1.18	1.03-1.35
	IHD or stroke unspecified	0	0	-	-
	IHD overall	3	4	1.18	1.03-1.35
	Myocardial infarction	2	2	1.17	1.01-1.34
	IHD unspecified	1	2	1.29	0.86-1.94
	IHD mortality	0	0	-	-
High efforts					
	CVD overall (IHD or stroke)	2	2	1.07	0.85-1.36
	IHD or stroke unspecified	0	0	-	-
	IHD overall	2	2	1.07	0.85-1.36
	Myocardial infarction	2	2	1.07	0.85-1.36
	IHD unspecified	0	0	-	-
	IHD mortality	0	0	-	-
Low reward					
	CVD overall (IHD or stroke)	2	2	1.11	0.92-1.34
	IHD or stroke unspecified	0	0	-	-
	IHD overall	2	2	1.11	0.92-1.34
	Myocardial infarction	2	2	1.11	0.92-1.34
	IHD unspecified	0	0	-	-
	IHD mortality	0	0	-	-

[1] Meta-analytic risk estimates are based on the fully adjusted risk estimates, minimally adjusted for sex, age and some measure of socio-economic position.
[2] The number of studies does not add up to total numbers because some studies contributed to more than one outcome.

Table 2c. Meta-analytic random effect risk estimates (RR)[1] for **JOB INSECURITY** and cardiovascular disease outcomes. Within-study stratified risk estimates were pooled (one risk estimate per study).

	Outcome	Studies[2] (N)	Estimates (N)	RR	95% CI
Job insecurity (yes versus no)					
	CVD overall	6	9	1.14	1.04-1.26
	IHD or stroke unspecified	0	0	-	-
	IHD overall	6	8	1.16	1.05-1.28
	Myocardial infarction	3	3	1.09	0.95-1.25
	IHD unspecified	4	5	1.24	1.07-1.42
	IHD mortality	0	0	-	-
	Stroke overall	1	1	0.94	0.63-1.40
	Ischemic stroke	1	1	0.94	0.63-1.40
	Haemorrhagic stroke	0	0	-	-
	Stroke unspecified	0	0	-	-
	Stroke mortality	0	0	-	-

[1] Meta-analytic risk estimates are based on the fully adjusted risk estimates, minimally adjusted for sex, age and some measure of socio-economic position.
[2] The number of studies does not add up to total numbers because some studies contribute to more than one specific outcome.

Table 2d. Meta-analytic random effect risk estimates (RR)[1] for **LONG WORKING WEEKLY HOURS** and cardiovascular disease outcomes. Within-study stratified risk estimates were pooled (one risk estimate per study). If risk was given by exposure level, only the highest level was used.

Exposure	Outcome	Studies[2] (N)	Estimates (N)	RR	95% CI
Weekly working hours: 41 -55 versus 35-40					
	CVD overall	8	16	1.02	0.93-1.12
	IHD or stroke unspecified	0	0	-	-
	IHD overall	5	8	1.01	0.88-1.15
	Myocardial infarction	2	2	1.11	0.79-1.57
	IHD unspecified	1	1	1.07	0.94-1.21
	IHD mortality	2	5	0.92	0.84-1.00
	Stroke overall	4	8	1.01	0.91-1.13
	Ischemic stroke	2	2	0.92	0.74-1.14
	Haemorrhagic stroke	2	2	1.31	1.02-1.68
	Stroke unspecified	2	2	1.08	0.92-1.27
	Stroke mortality	1	2	0.94	0.80-1.10
Weekly working hours 55+ versus 35-40 [3]					
	CVD overall (IHD or stroke)	8	20	1.09	0.91-1.13
	IHD or stroke unspecified	0	0	-	-
	IHD overall	5	9	1.23	0.88-1.72
	Myocardial infarction	2	2	2.06	1.21-3.52
	IHD unspecified	1	1	0.87	0.68-1.12
	IHD mortality	2	6	1.01	0.86-1.19
	Stroke overall	5	11	1.01	0.87-1.16
	Ischemic stroke	2	2	0.90	0.69-1.17
	Haemorrhagic stroke	2	2	0.93	0.46-1.91
	Stroke unspecified	2	2	1.07	0.75-1.53
	Stroke mortality	2	5	0.97	0.82-1.15

[1] Meta-analytic risk estimates are based on the fully adjusted risk estimates, minimally adjusted for sex, age and some measure of socio-economic position.
[2] The number of studies does not add up to total numbers because some studies contribute to more than one outcome.
[3] Includes Kivimäki et al 2015 (10 unpublished IPD studies) where weekly working hours were dichotomised into >= 55 hours/week versus not.

Table 3a. Fully adjusted random-effect relative risk (RR)[1] for **JOB STRAIN** and **CARDIOVASCULAR DISEASE** (ischemic heart disease or stroke) by study characteristics and subgroups. Multiple risk estimates within studies were averaged before calculation of meta-analytic risk estimates.

Exposure	Characteristic	Studies (N)	Estimates (N)	RR	95% CI
Country					
	Nordic	10	18	1.08	0.99-1.18
	Other	16	31	1.16	1.06-1.26
Population					
	Occupational	12	21	1.19	1.11-1.28
	Other	14	28	1.08	1.00-1.17
	Only men	6	12	1.16	1.04-1.29
	Only women	6	9	1.17	0.93-1.48
Exposure ascertainment					
	Self-report	17	32	1.16	1.04-1.29
	Job exposure matrix	7	15	1.08	1.00-1.17
	Other	2	2	1.40	0.99-1.98
Outcome ascertainment					
	Hospital diagnosis or death registry	16	30	1.11	1.04-1.19
	Other	10	19	1.19	1.02-1.40
Baseline response rate					
	< 75%	11	22	1.31	1.11-1.55
	75-100%	7	11	1.09	1.00-1.19
	Missing	8	16		
Entry year					
	1970-1989	11	23	1.16	1.10-1.22
	1990+	15	26	1.12	0.99-1.27
Follow-up duration, years					
	1-10	8	10	1.09	0.98-1.21
	>10	16	35	1.16	1.05-1.29
	Missing	2	4		
Sample size					
	<500	9	12	1.17	0.97-1.41
	500+	13	28	1.11	1.03-1.19
	Missing	4	9		
Control for mediators[2]					
	Yes, fully adjusted	16	28	1.11	1.02-1.21
	Yes, crude	16	28	1.22	1.11 -1.34
	Unspecified	10	21	1.17	1.05-1.13
Sex strata					
Within and between studies	Men	15	23	1.15	1.08-1.23
	Women	15	20	1.15	1.00-1.33

	Unspecified	5	6	1.09	0.98-1.20
Social strata					
Within and between	White collar	10	15	1.27	1.09-1.47
	Blue collar	5	8	1.22	1.04-1.45
	Unspecified	15	26	1.08	1.01-1.15
Job strain adjusted for demand and control					
	Yes, fully adjusted[3]	4	5	1.08	0.89-1.31
	Yes, crude[4]	4	5	1.26	0.98-1.63
	Unspecified[5]	22	44	1.16	1.08-1.26

[1] Minimally adjusted for sex, age and some measure of socio-economic position.
[2] Only studies with adjustment for behavioural and/or medical CVD risk factors (minimally adjusted and fully adjusted RR for these studies).
[3] Only studies that adjust job strain for demand and control.
[4] Same studies as 3 but minimally adjusted risk estimates to allow evaluation of effect of adjustment.
[5] Studies that do not control for demand and control.

Table 3b. Fully adjusted random-effect relative risk (RR)[1] for **JOB STRAIN** and **ISCHEMIC HEART DISEASE** by study characteristics and subgroups. Multiple risk estimates within studies were averaged before calculation of meta-analytic risk estimates.					
Exposure	Characteristic	Studies (N)	Estimates (N)	RR	95% CI
Country					
	Nordic	7	10	1.09	0.99-1.19
	Other	14	22	1.14	1.04-1.25
Population					
	Occupational	10	13	1.16	1.08-1.25
	Other	11	19	1.09	1.00-1.20
	Only men	6	9	1.19	1.03-1.38
	Only women	4	5	1.07	0.80-1.43
Exposure ascertainment					
	Self-report	13	20	1.18	1.06-1.32
	Job exposure matrix	7	11	1.06	0.99-1.13
	Other	1	1	1.30	0.85-1.99
Outcome ascertainment					
	Hospital diagnosis or death registry	13	20	1.11	1.04-1.19
	Other	8	12	1.19	1.02-1.40
Baseline response rate					
	< 75%	7	12	1.38	1.19-1.60
	75-100%	7	8	1.09	0.99-1.20
	Missing	7	12		
Entry year					
	1970-1989	10	16	1.15	1.08-1.22
	1990+	11	16	1.09	0.97-1.24
Follow-up duration, years					
	1-10	6	7	1.08	0.95-1.22
	>10	13	21	1.16	1.05-1.28
	Missing	2	4		
Sample size					
	<500	9	12	1.17	0.97-1.41
	500+	12	20	1.11	1.03-1.19
	Missing	0	0	-	-
Control for potential mediators[2]					
	Yes, fully adjusted	14	20	1.12	1.03-1.23
	Yes, crude	14	20	1.24	1.14-1.35
	Unspecified	7	12	1.12	1.01-1.25
Sex strata					
Within and between studies	Men	13	16	1.16	1.08-1.25
	Women	11	12	1.10	0.94-1.28
	Unspecified	4	4	1.09	0.96-1.24

Social strata					
Within and between studies	White collar	8	10	1.25	1.08-1.45
	Blue collar	4	4	1.24	1.02-1.50
	Unspecified	12	18	1.06	1.00-1.13
Job strain adjusted for demand and control					
	Yes, fully adjusted[3]	4	5	1.14	0.94-1.38
	Yes, crude[4]	4	5	1.37	1.11-1.70
	Unspecified[5]	17	27	1.12	1.04-1.20

[1] Minimally adjusted for sex, age and some measure of socio-economic position.
[2] Only studies with adjustment for behavioural and/or medical CVD risk factors (minimally adjusted and fully adjusted RR in these studies).
[3] Only studies that adjust job strain for demand and control.
[4] Same studies as 3 but minimally adjusted risk estimates to allow evaluation of effect of adjustment.
[5] Studies that do not control for demand and control.

Table 3c. Fully adjusted random-effect relative risk (RR)[1] for **VERY LONG WORKING HOURS (55+ hours/week versus 35-40 hours/week)** and **CARDIOVASCULAR DISEASE** by study characteristics and subgroups. Multiple risk estimates within studies were averaged before calculation of meta-analytic risk estimates.

Exposure	Characteristic	Studies (N)	Estimates (N)	RR	95% CI
Country					
	Nordic	1	3	0.94	0.78-1.14
	Other	7	22	1.14	0.91-1.43
Population					
	Occupational	2	4	1.19	0.68-2.08
	Other	6	21	1.08	0.88-1.33
	Only men	2	3	1.48	0.42-5.20
	Only women	0	0	-	-
Exposure ascertainment					
	Self-report	7	24	1.02	0.90-1.17
	Job exposure matrix	0	0	-	-
	Other	1	1	2.94	1.39-6.23
Outcome ascertainment					
	Hospital diagnosis or death registry	6	23	0.99	0.89-1.09
	Other	2	2	2.06	1.21-3.52
Baseline response rate					
	< 75%	4	6	1.09	0.85-1.40
	75-100%	2	6	0.95	0.89-1.02
	Missing	2	13		
Entry year					
	1970-1989	0	0	-	-
	1990+	8	25	1.09	0.91-1.30
Follow-up duration, years					
	1-10	3	19	0.96	0.91-1.03
	>10	2	3	1.14	0.57-2.31
	Missing	3	3		
Sample size					
	<500	2	2	2.06	1.21-3.52
	500+	3	17	0.96	0.90-1.02
	Missing	3	6		
Control for mediators[2]					
	Yes, fully adjusted	3	4	1.50	0.73 -3.09
	Yes, crude	3	4	1.62	0.80-3.28
	Not controlling	5	21	1.01	0.89-1.13
Sex strata					
Within and between studies	Men	4	12	1.15	0.75-1.77
	Women	2	7	1.15	0.87-1.52
Social strata		4	6	1.09	0.85-1.40
Within and between studies	White collar	2	10	1.24	0.75-2.05
	Blue collar	1	3	1.79	1.19-2.71
	Other	6	12	1.01	0.87-1.17

[1] Minimally adjusted for sex, age and some measure of socio-economic position.

[2] Only studies with adjustment for behavioural and/or medical CVD risk factors)minimally adjusted and fully adjusted RR in these studies).

able 3d. Fully adjusted random-effect relative risk (RR)[1] for **VERY LONG WORKING HOURS (55+ H/W VERSUS 35-40 H/W)** and **ISCHEMIC HEART DISEASE** by study characteristics and subgroups. Multiple risk estimates within studies averaged before calculation of meta-analytic risk estimates.

Exposure	Characteristic	N Studies	N Estimates	RR	95% CI
Country					
	Nordic	0	0	-	-
	Other	5	12	1.23	0.88-1.72
Population					
	Occupational	1	1	1.67	1.02-2.75
	Other	4	11	1.14	0.79-1.67
	Only men	1	1	2.94	1.39-6.23
	Only women	0	0	-	-
Exposure ascertainment					
	Self-report	4	11	1.04	0.86-1.26
	Job exposure matrix	0	0	-	-
	Other	1	1	2.94	1.39-6.23
Outcome ascertainment					
	Hospital diagnosis or death registry	3	10	0.97	0.88-1.07
	Other	2	2	2.06	1.21-3.52
Baseline response rate					
	< 75%	2	2	1.16	0.62-2.19
	75-100%	1	2	0.96	0.86-1.08
	Missing	2	8		
Entry year					
	1970-1989	0	0	-	-
	1990+	5	12	1.23	0.88-1.72
Follow-up duration, years					
	1-10	2	9	1.01	0.86-1.19
	>10	1	1	1.67	1.02-2.75
	Missing	2	2	-	-
Sample size					
	<500	2	2	2.06	1.21-3.52
	500+	3	10	0.97	0.88-1.07
	Missing	0	0	-	-
Control for mediators[2]					
	Yes, fully adjusted	2	2	2.06	1.21-3.52
	Yes, crude	2	2	2.22	1.47-3.35
	Not controlling	3	10	0.97	0.88-1.07
Sex strata					
Within and between studies	Men	3	6	1.33	0.74-2.40
	Women	2	4	1.23	0.85-1.78
	Other	2	2	1.16	0.62-2.19
Social strata					
Within and between studies	White collar	2	6	1.26	0.77-2.05
	Blue collar	1	2	1.55	1.10-2.18
	Other	3	4	1.24	0.64-2.39

[1] Minimally adjusted for sex, age and some measure of socio-economic position.

[2] Only studies with adjustment for behavioural and/or medical CVD risk factors – fully adjusted and minimally adjusted RR.

FIGURES: OVERVIEW

Forest plots of fully adjusted hazard ratio of associations between psychosocial exposures and cardiovascular disease outcomes in 57 follow-up and 2 case-control studies with 315 risk estimates that were included in the current review.

1. Job strain
2. Job demands
3. Job control
4. Workplace support
5. Isostrain
6. Effort-reward imbalance
7. Efforts
8. Rewards
9. Job insecurity
10. Long working hours, 40-55 hours/week
11. Long working hours, 55+ hours/week

Figure 1a. Forest plot of associations between **HIGH JOB STRAIN** and cardiovascular disease outcomes including risk estimates stratified by subgroups. Relative risk (HR, RR or OR) and 95% confidence limits. Abbreviations are given in Annex I.

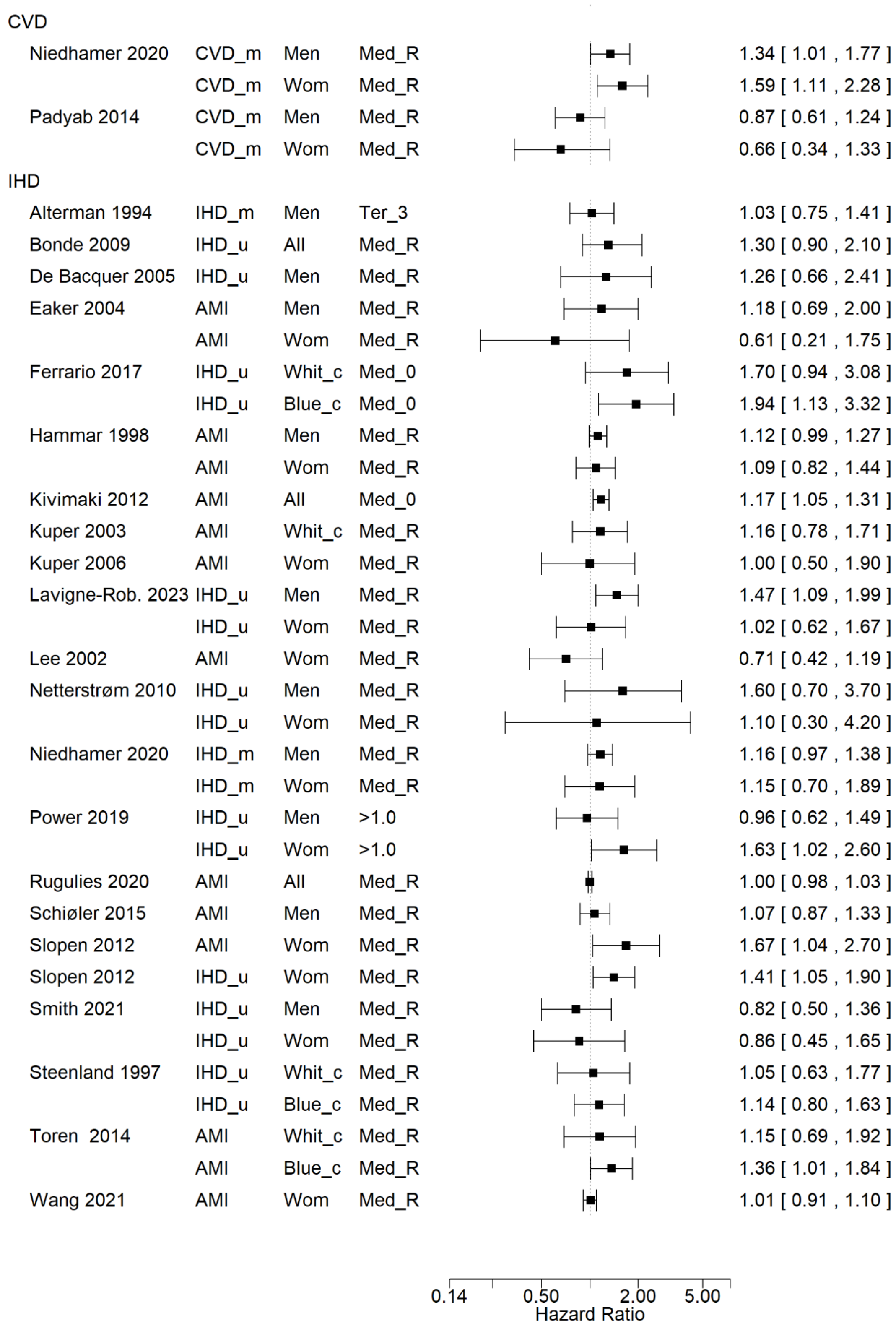


Figure 1a continued.

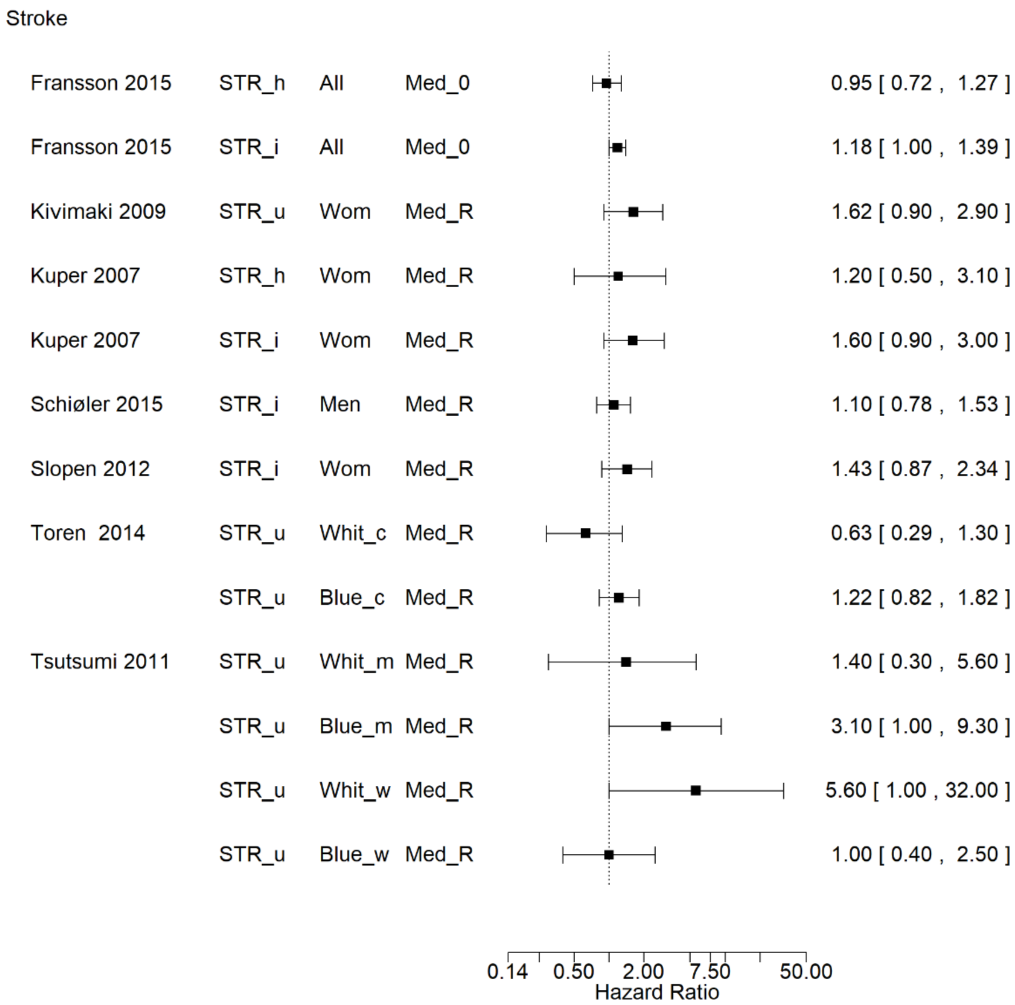


Figure 1b Funnel plot of associations between **HIGH JOB STRAIN** and ischemic heart disease in eligible published studies.

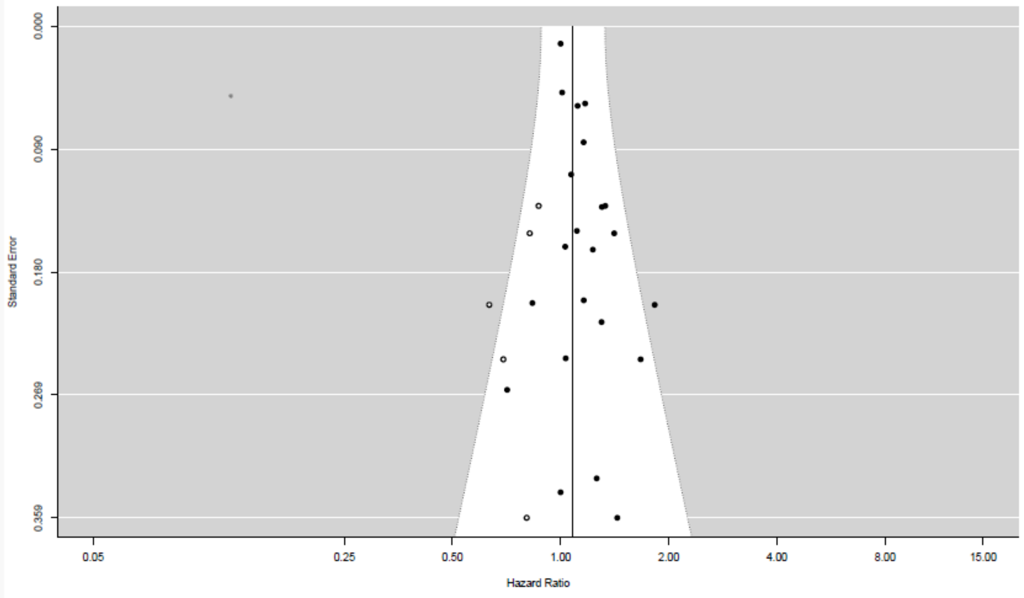


Figure 2. Forest plot of associations between **HIGH ISOSTRAIN** and cardiovascular disease outcomes including stratified risk estimates and estimates by exposure levels. Relative risk (HR, RR or OR) and 95% confidence limits. Abbreviations are given in Annex I.

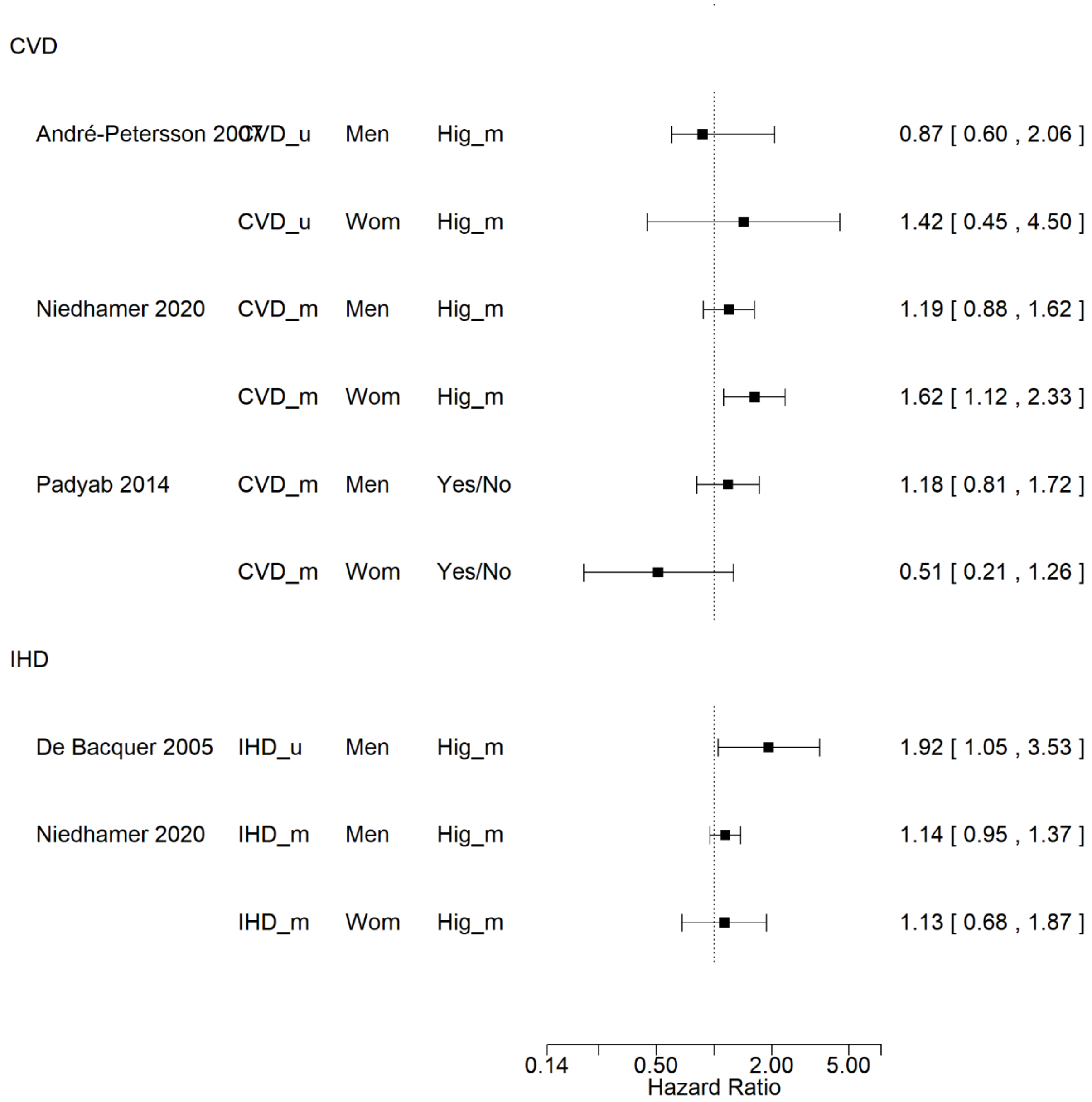


Figure 3. Forest plot of associations between **HIGH JOB DEMANDS** and cardiovascular disease outcomes including stratified risk estimates and estimates by exposure level. Relative risk (HR, RR or OR) and 95% confidence limits. Abbreviations are given in Annex I.

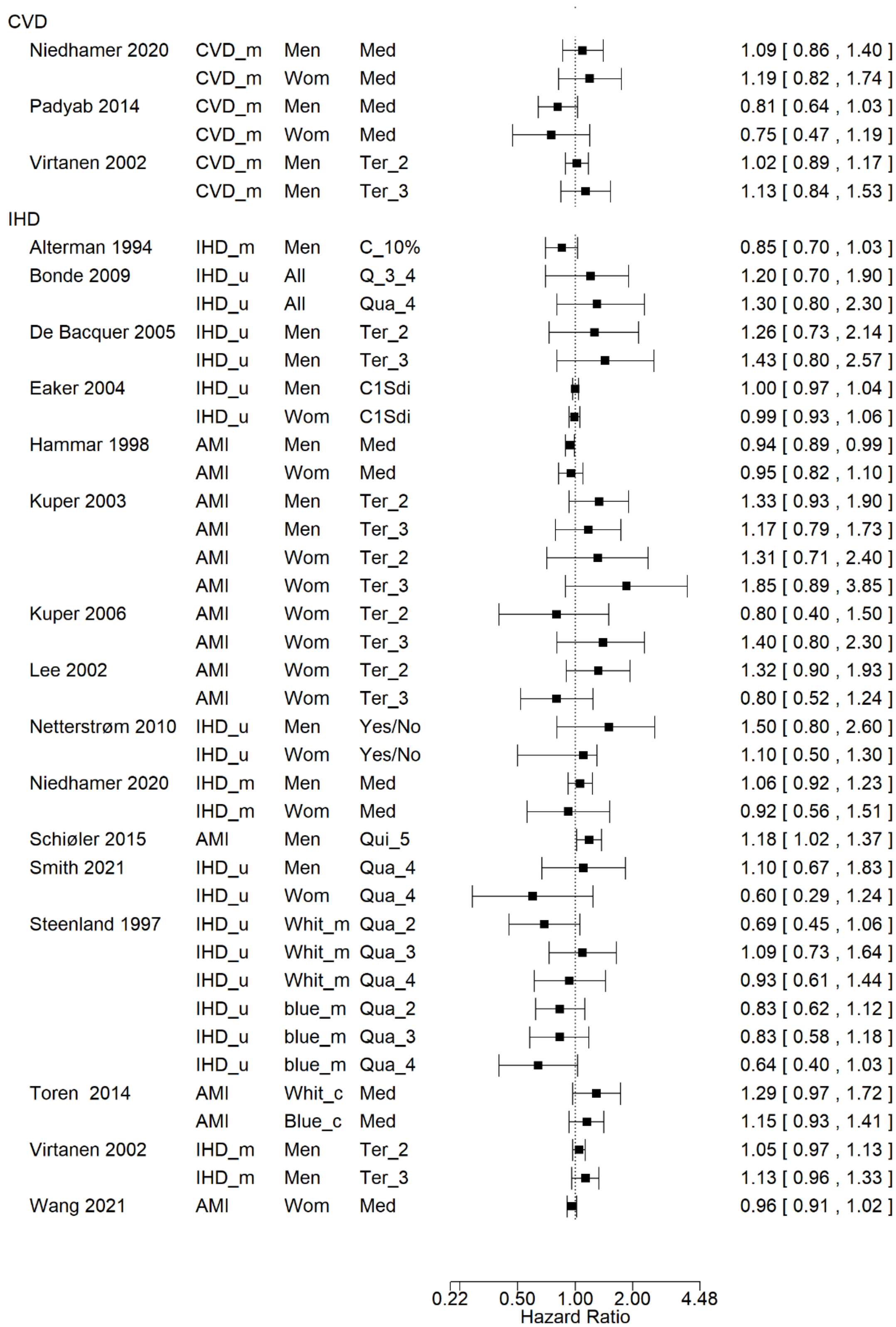


Figure 3 continued.

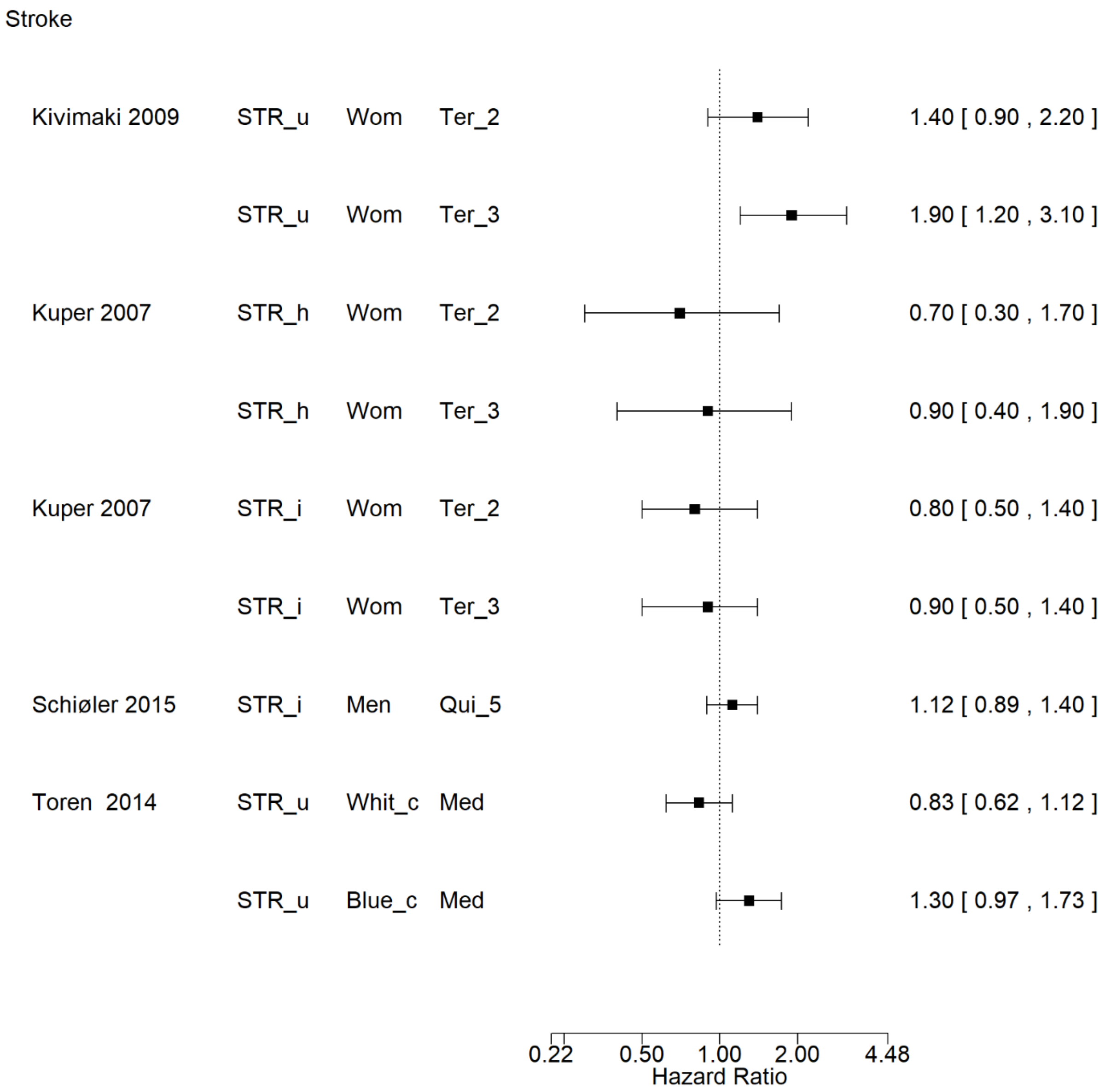


Figure 4. Forest plot of associations between **LOW JOB CONTROL** and cardiovascular disease outcomes including stratified risk estimates and estimates by exposure levels. Relative risk (HR, RR or OR) and 95% confidence limits. Abbreviations are given in Annex I.

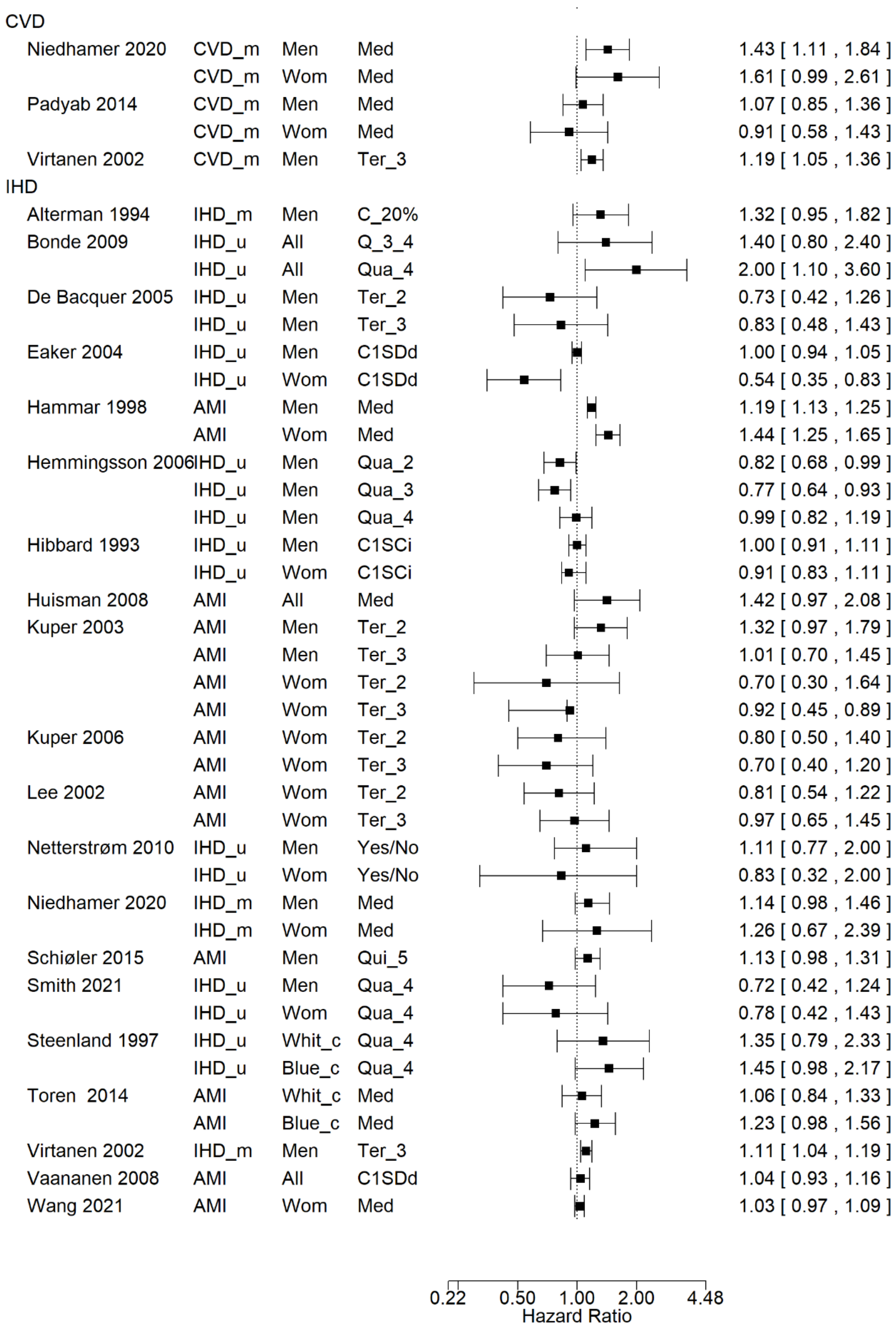


Figure 4 continued.

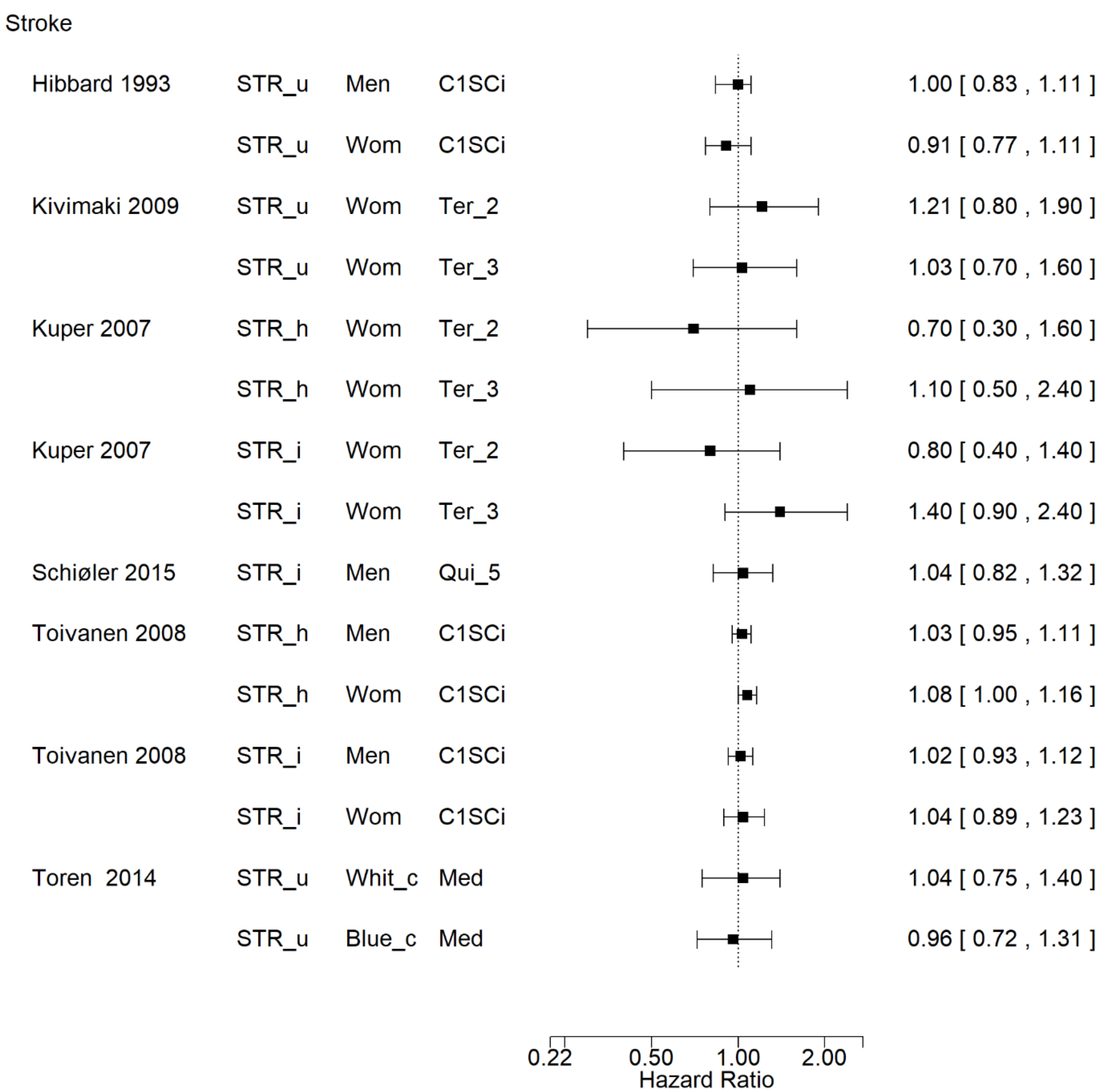

Stroke
Hibbard 1993 STR_u Men C1SCi 1.00 [0.83 , 1.11]
STR_u Wom C1SCi 0.91 [0.77 , 1.11]
Kivimaki 2009 STR_u Wom Ter_2 1.21 [0.80 , 1.90]
STR_u Wom Ter_3 1.03 [0.70 , 1.60]
Kuper 2007 STR_h Wom Ter_2 0.70 [0.30 , 1.60]
STR_h Wom Ter_3 1.10 [0.50 , 2.40]
Kuper 2007 STR_i Wom Ter_2 0.80 [0.40 , 1.40]
STR_i Wom Ter_3 1.40 [0.90 , 2.40]
Schiøler 2015 STR_i Men Qui_5 1.04 [0.82 , 1.32]
Toivanen 2008 STR_h Men C1SCi 1.03 [0.95 , 1.11]
STR_h Wom C1SCi 1.08 [1.00 , 1.16]
Toivanen 2008 STR_i Men C1SCi 1.02 [0.93 , 1.12]
STR_i Wom C1SCi 1.04 [0.89 , 1.23]
Toren 2014 STR_u Whit_c Med 1.04 [0.75 , 1.40]
STR_u Blue_c Med 0.96 [0.72 , 1.31]
0.22
0.50
1.00
2.00
Hazard Ratio

Figure 5. Forest plot of associations between **LOW SOCIAL SUPPORT** and cardiovascular disease outcomes including stratified risk estimates and estimates by exposure levels. Relative risk (HR, RR or OR) and 95% confidence limits. Abbreviations are given in Annex I.

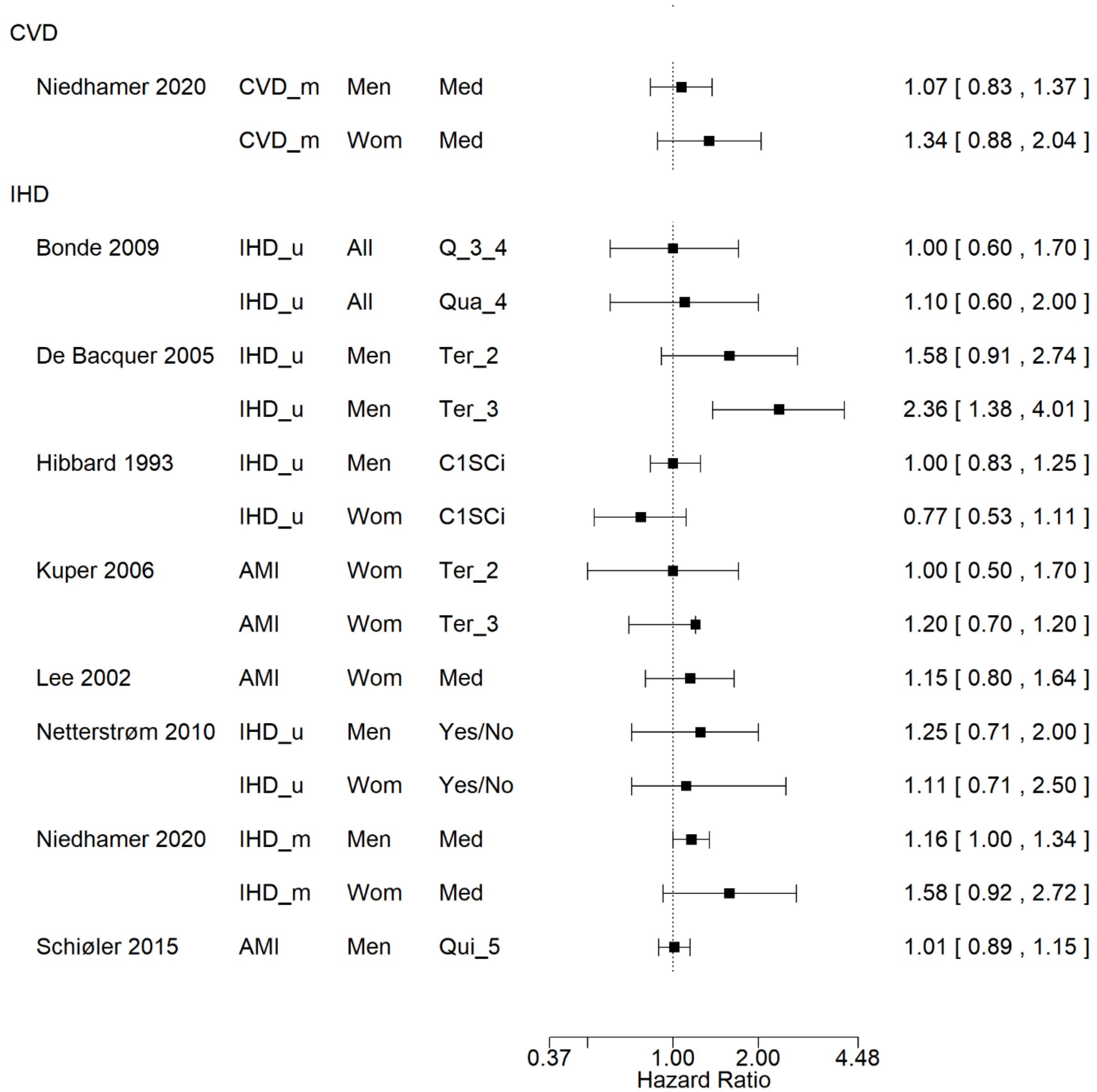


Figure 5 continued.

Stroke

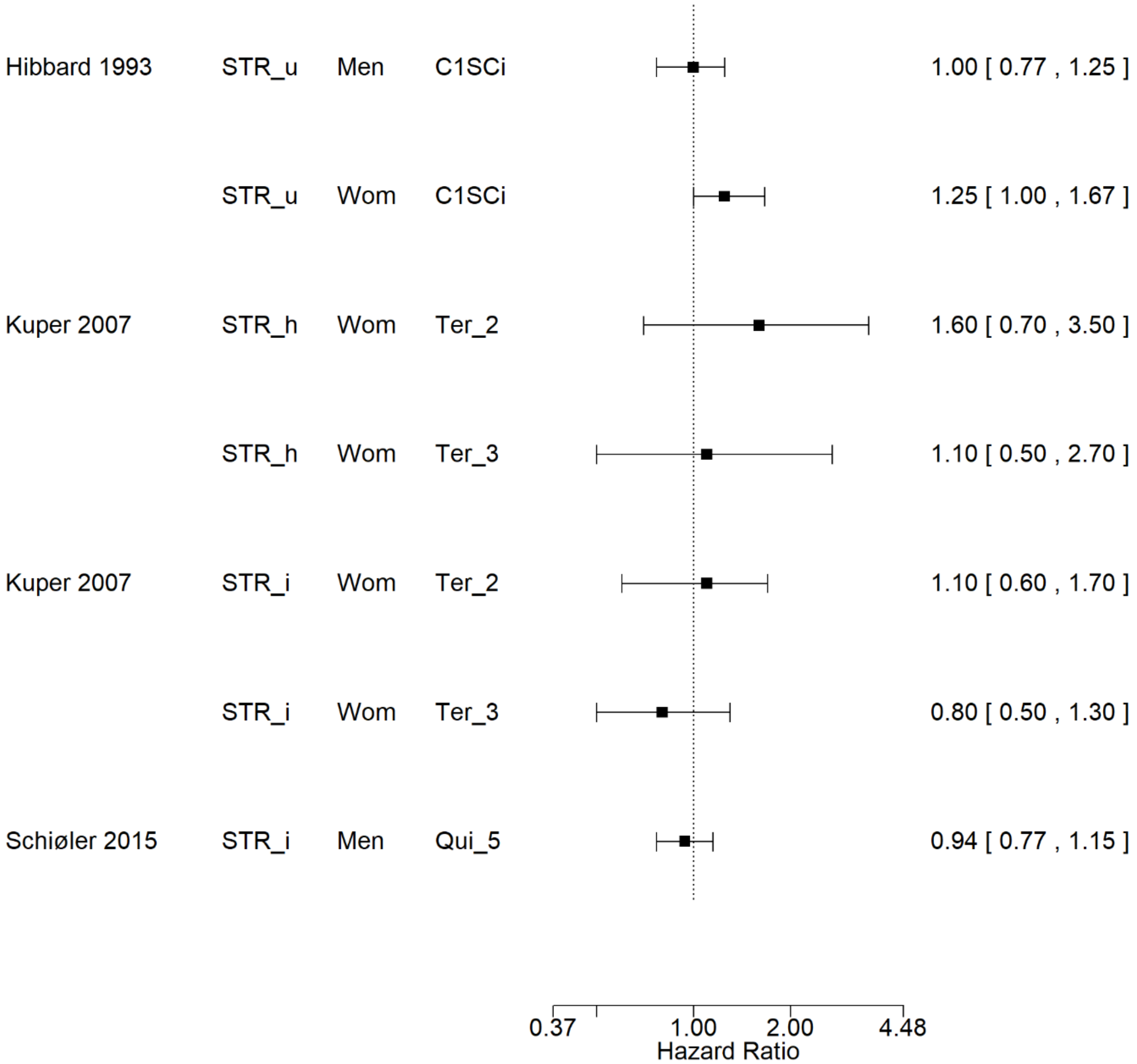

Hibbard 1993 STR_u Men C1SCi 1.00 [0.77 , 1.25]
STR_u Wom C1SCi 1.25 [1.00 , 1.67]
Kuper 2007 STR_h Wom Ter_2 1.60 [0.70 , 3.50]
STR_h Wom Ter_3 1.10 [0.50 , 2.70]
Kuper 2007 STR_i Wom Ter_2 1.10 [0.60 , 1.70]
STR_i Wom Ter_3 0.80 [0.50 , 1.30]
Schiøler 2015 STR_i Men Qui_5 0.94 [0.77 , 1.15]
0.37
1.00
2.00
4.48
Hazard Ratio

Figure 6. Forest plot of associations between **EFFORT-REWARD IMBALANCE** and cardiovascular disease outcomes including stratified risk estimates and estimates by exposure levels. Relative risk (HR, RR or OR) and 95% confidence limits. Abbreviations are given in Annex I.

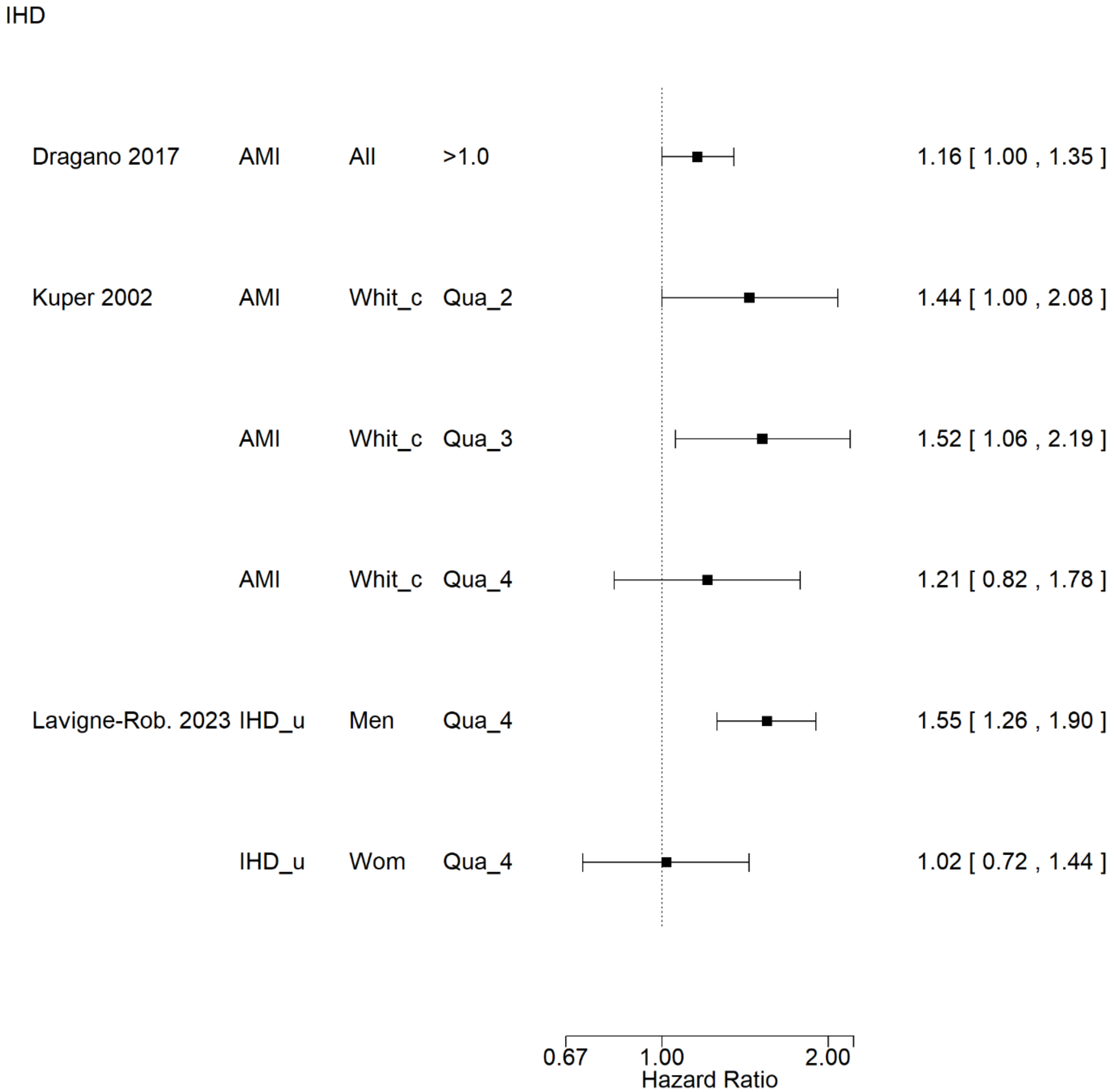


Figure 7. Forest plot of associations between **HIGH EFFORTS** and cardiovascular disease outcomes including stratified risk estimates and estimates by exposure levels. Relative risk (HR, RR or OR) and 95% confidence limits. Abbreviations are given in Annex I.

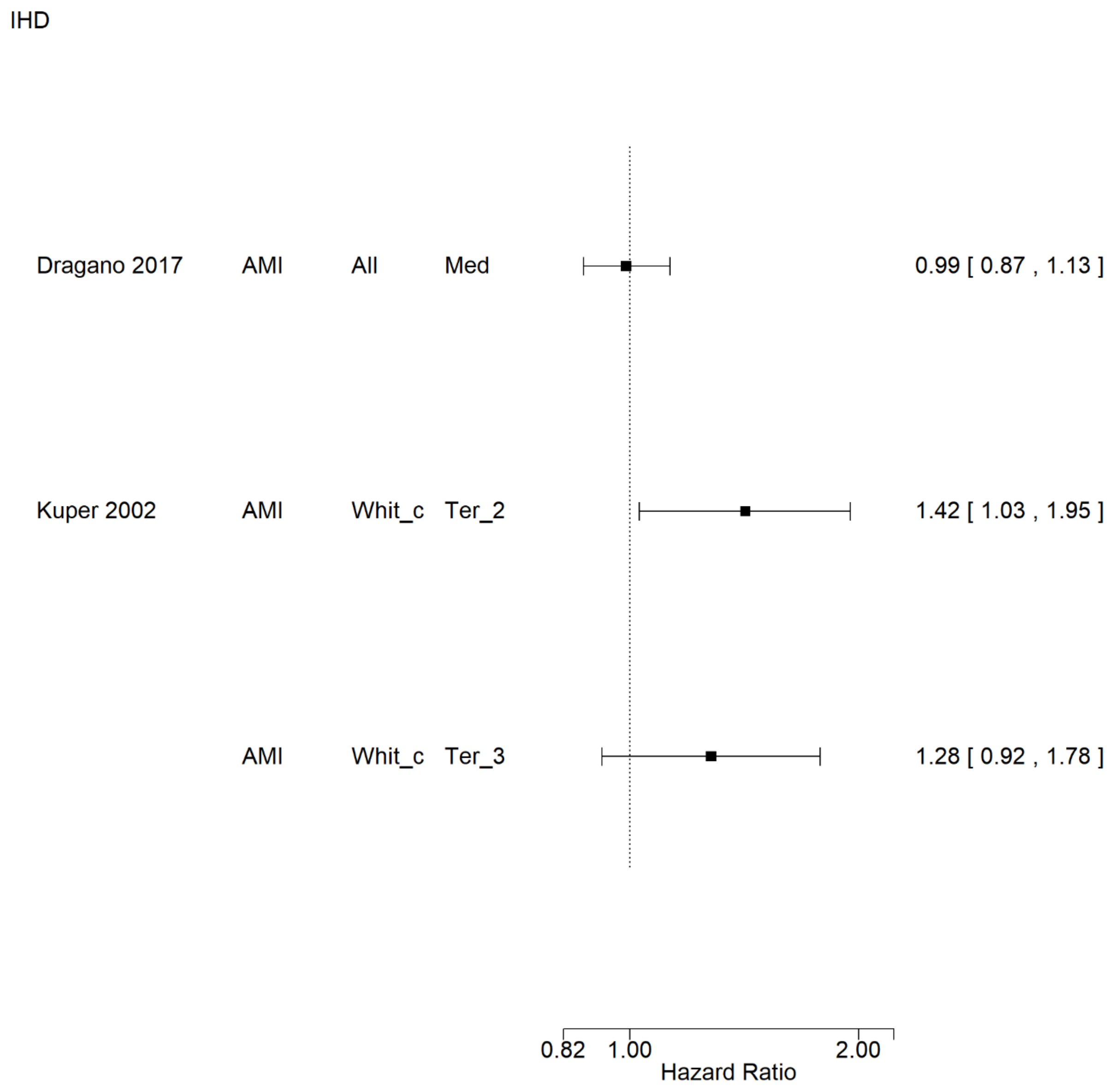


Figure 8. Forest plot of associations between **LOW REWARDS** and cardiovascular disease outcomes including stratified risk estimates and estimates by exposure levels. Relative risk (HR, RR or OR) and 95% confidence limits. Abbreviations are given in Annex I.

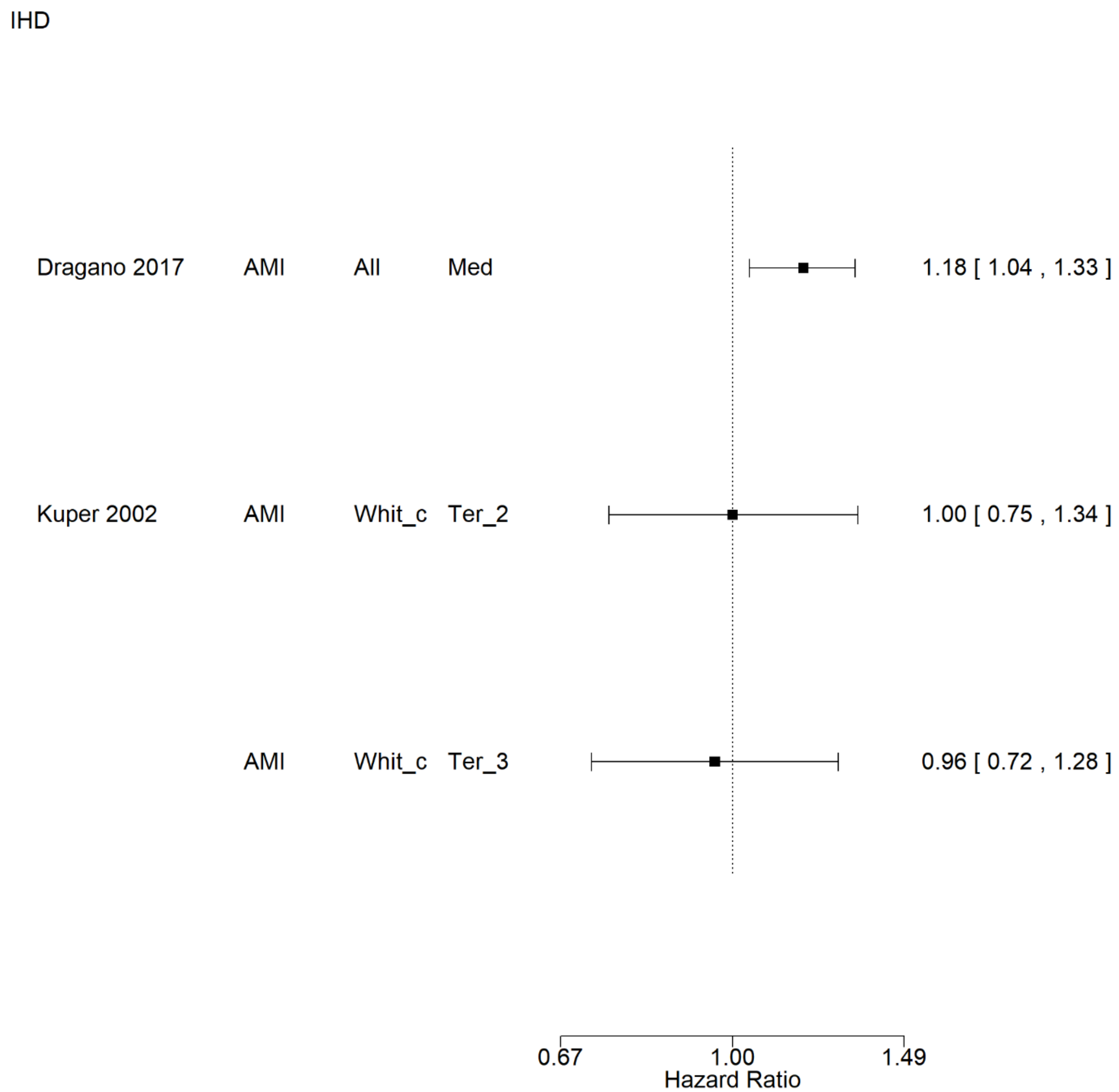


Figure 9. Forest plot of associations between **JOB INSECURITY** and cardiovascular disease outcomes including stratified risk estimates. Relative risk (HR, RR or OR) and 95% confidence limits. Abbreviations are given in Annex I.

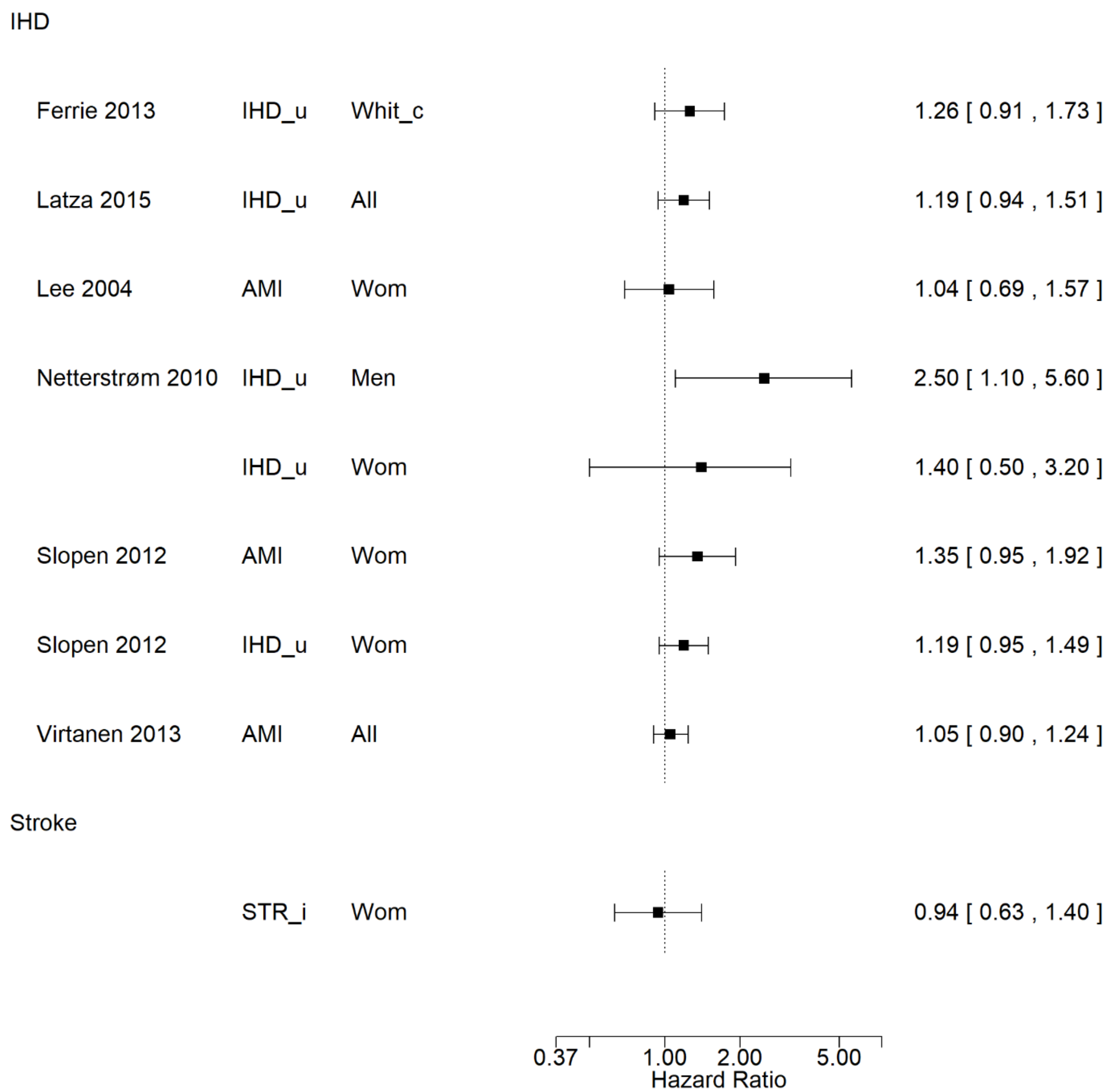


Figure 10. Forest plot of associations between **MODERATELY LONG WORKING HOURS (41-55 HOURS /WEEK VERSUS 35-40 HOURS/WEEK)** and cardiovascular disease outcomes including stratified risk estimates and estimates by exposure levels. Relative risk (HR, RR or OR) and 95% confidence limits. Abbreviations are given in Annex I.

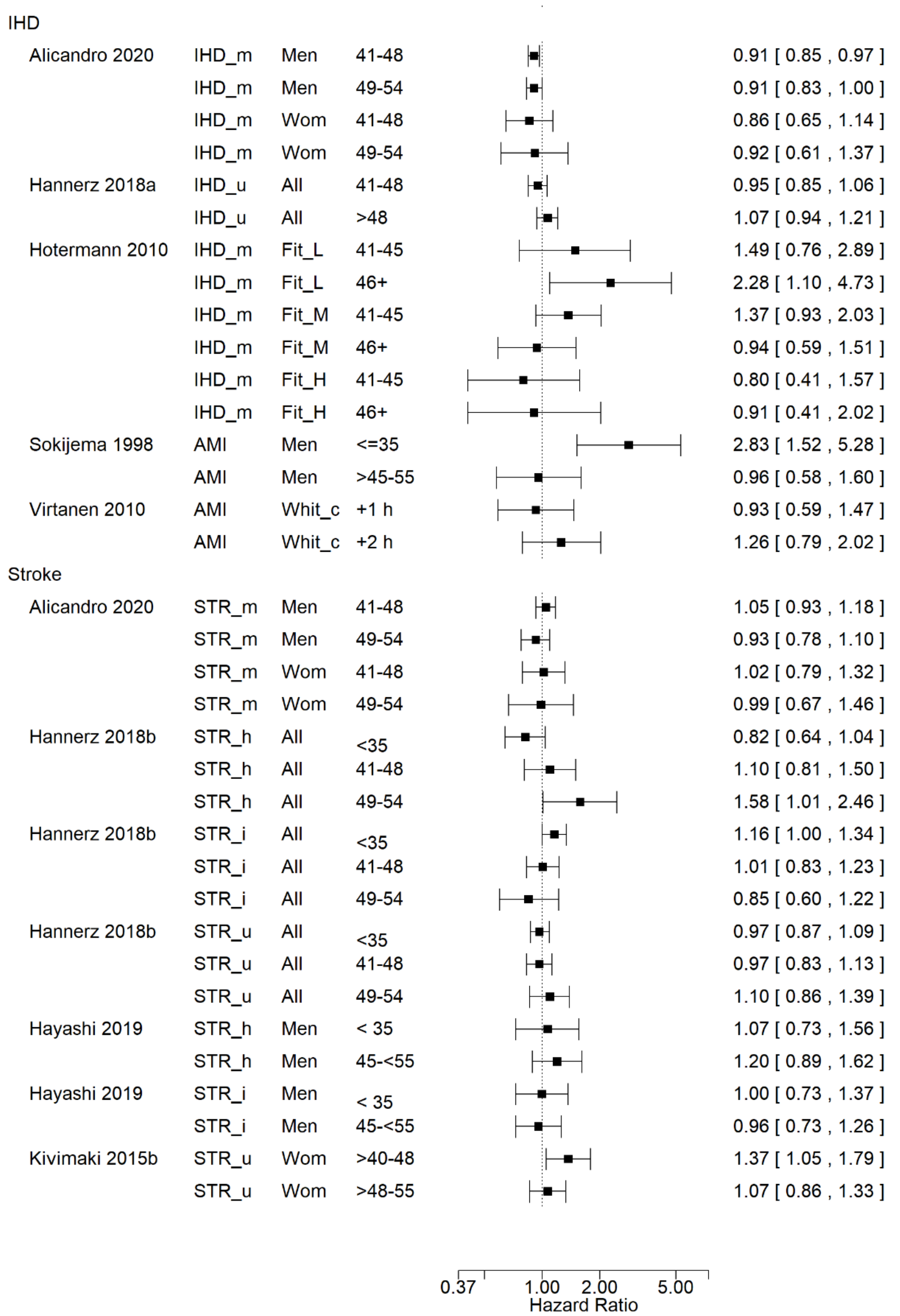
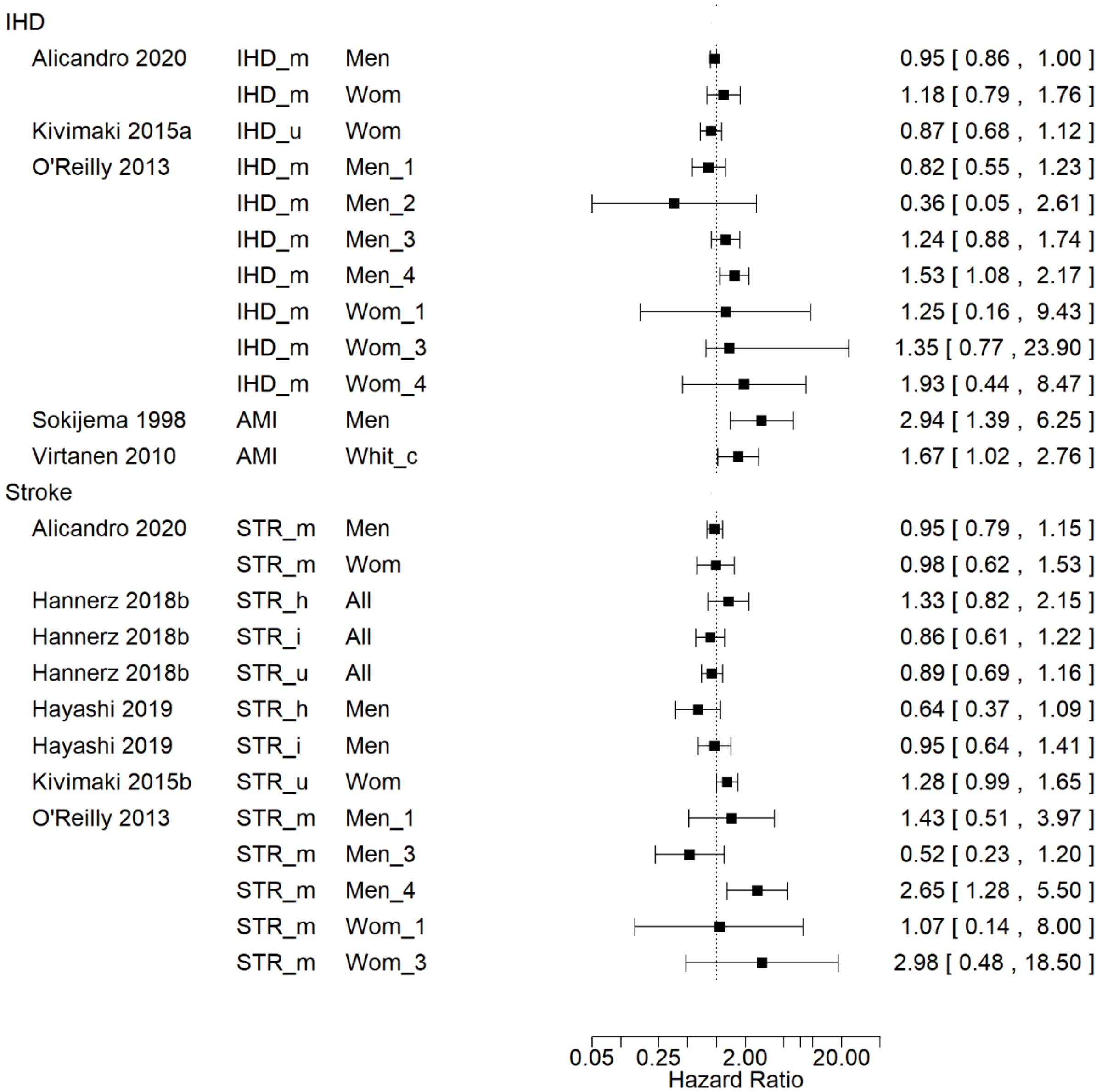


Figure 11. Forest plot of associations between **VERY LONG WORKING HOURS (55+ HOURS/WEEK VERSUS 35-40 HOURS/WEEK)** and cardiovascular disease outcomes including stratified risk estimates and estimates by exposure levels. Relative risk (HR, RR or OR) and 95% confidence limits. Abbreviations are given in Annex I.



ANNEX I: List of abbreviations and terminology in text, tables and forest plots

Strength of associations (RR, OR, HR)

Small/weak	1.00 – 1.25
Modest	1.26 – 1.50
Medium	1.51 – 2.00
Large	> 2.00

SelfAQ	Self-administered questionnaire
JCQ	Job content questionnaire
JCS	Demand-control-support (work stress model, am Karasek)
ERI	Effort-reward imbalance (model, am Siegrist)
JEM	Job exposure matrix
ICD-10	International classification of diseases 10th edition or equivalent codes in ICD-8 and ICD-9

IPD Consortium Individual participant data Consortium, a European research network doing meta-analyses based upon unpublished cohorts with harmonized individual data

CBV Cerebrovascular disease: Stroke unspecified: ICD-10: I60-I 69 and ICD-8-9: 430-38. Ischemic stroke ICD-10: I63.3-I63.9. Intracerebral haemorrhage ICD-10: I61

CVD	Cardiovascular disease (IHD or CBV)
IHD	Ischemic heart disease (ICD-10: I20-I25, ICD-8-9: 410)
MI	Myocardial infarction (ICD-10: I21, ICD-8-9: 410-414)
CI	Confidence interval
HR	Hazard ratio
OR	Odds ratio
NR	Not reported
NA	Not applicable

Ischaemic heart diseases:

ICD-10: I20-I25 (including angina pectoris but not hypertension, ICD-8,9: 410-410

Myocardial infarction:

ICD-10: I21 (and I22) most often also include fatal IHD (ICD-10: I20-I25 or unspecified) because first manifestation of a minor fraction of MI is sudden death, e.g. Lee 2004.

Stroke:

ICD-10: I60--I69 (haemorrhagia subarachnoidalis and cerebri, infarktus cerebri), ICD-8,9: 430-432, 433-434, 436)

JEM survey Job exposure matrix based upon independent occupational surveys of self-reported workplace psychosocial exposures. Job specific item scores are assigned on the basis of the job title at baseline unless otherwise specified.

JEM expert Job exposure matrix based upon independent expert assessment, observations, and measurements.

Job strain, quadrant, median, high vs low:

Combination of high demands and low control defined by median scale sumscore in which high strain is compared with low strain (low demands and high control)

Job strain, quadrant, median, high vs all:

Combination of high demands and low control defined by median scale sumscore in which high strain is compared with all other demand/control combinations.

Job strain, quadrant, tertiles high vs low:

Combination of high demands and low control defined by tertiles of item sum score in which high strain (highest tertile of demand and low/intermediate control) is compared with low strain (low demands and high control)

Job strain ratio method:

ratio of demand and inversed control item scores dichotomised >=1 (highest strain) and <1 (lowest strain)

Isostrain, quadrant, median split:

job strain combined with low social support at work (median split), high isostrain vs low isostrain.

Abbreviations in forest plots

Outcomes

AMI	AMI
IHD_u	IHD unspecified
IHD_m	IHD mortality
STR_u	Stroke unspecified
STR_i	Ischemic stroke
STR_h	Haemorrhagic stroke
STR_m	Stroke mortality
CVD_u	IHD or stroke morbidity
CVD_m	IHD or stroke mortality

Strata within studies

Fit_l	Low physical fitness (lowest quintile)
Fit_m	Medium physical fitness (3 intermediate quintiles)
Fit_h	High physical fitness (highest quintile)
Men_1	Male managers
Men_2	Male intermediate jobs
Men_3	Male own accounts
Men_4	Male routine job
Wom_1	female managers
Wom_2	Female intermediate jobs

Wom_3	Female own accounts
Wom_4	Female routine job
White_c	White collar
Blue_c	Blue collar
White_m	Male white collar
Blue_m	Male blue collar
White_w	Female white collar
Blue_w	Female blue collar

Exposure contrast

Med_R	High versus low job train defined by median scale score, quadrant method, median split, strain versus relaxed
Med_0	High versus low job strain defined by median scale score, quadrant method, median split strain versus all others
Ter_2	Second versus lowest tertile of scale scores
Ter_3	Third versus lowest tertile of scale scores
Qua_2	Second versus lowest quartile of scale scores
Qua_3	Third versus lowest quartile of scale scores
Qua_4	Fourth versus lowest quartile of scale scores
Q_3_4	Third or fourth versus lowest quartile of scale scores
Qui_5	Fifth versus lowest quintile of scale scores
C_10%	Continuous scale score, 10% increment
C_20%	Continuous scale score, 20% increment
C1Sdi	Continuous scale score, 1 SD increment
C1SDd	Continuous scale score, 1 SD decrease
C1SCi	Continuous, 1 scale score increment
>1.0	Job strain score or ERI ratio >=1.0 versus < 1.0
Med	Scale score above median versus <= median
Hig_m	High isostrain (high strain and low support, median split)
Ye/no	Yes versus no, unspecified (no scale)

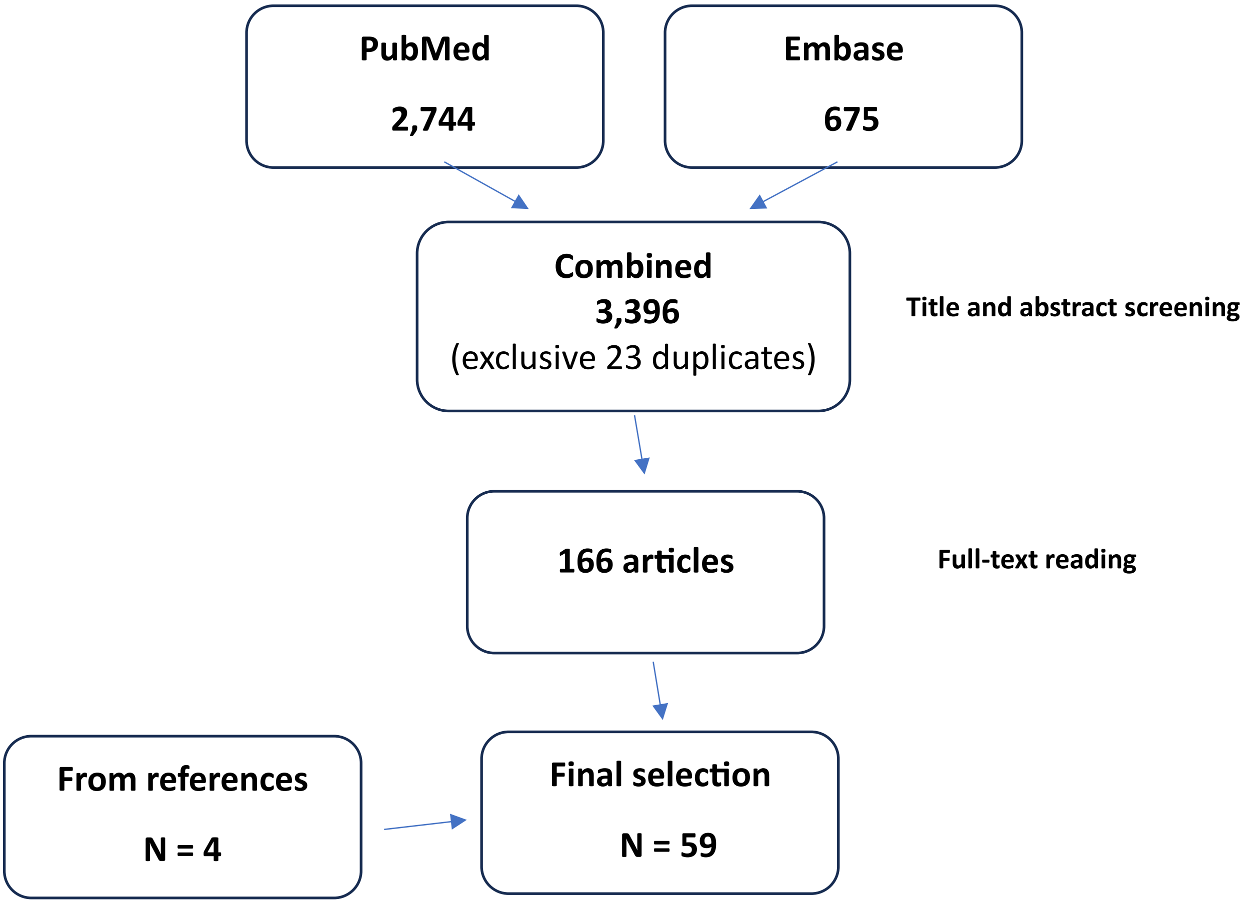
ANNEX II: PubMed and Embase Search strings

PubMed 15.11.2024		
Search	Query	Results
#1 Design	**cohort studies[MeSH] OR prospective studies[MeSH] OR longitudinal studies[MeSH] OR cross over studies[MeSH] OR controlled clinical trial[Publication Type] OR cohort[Tiab] OR prospective[Tiab] OR longitudinal[Tiab] OR cross sectional studies[MeSH] OR case-control studies[MeSH] OR cross-sectional[Tiab] OR cross sectional[Tiab] OR case-control[Tiab] OR case control[Tiab] OR case-referent[Tiab] OR case referent[Tiab] OR surveys and questionnaires/epidemiology[MeSH] OR survey[Tiab] OR case-crossover[Tiab] OR case crossover[Tiab] OR case-only[Tiab] OR intervention[Tiab] OR job exposure matrix[tiab] OR job-exposure matrix[tiab] or JEM[tiab]** Filters: **English, Humans, Adult: 19+ years**	2,969,381
#2 Exposure, MeSH	**occupational stress [Mesh] OR social capital[MeSH] OR job security[Mesh] OR job satisfaction[Mesh] OR occupational violence[Mesh] OR occupational bullying[Mesh] NOT editorial[publication type] NOT letter[publication type] NOT review[publication type] NOT systematic review[publication type]** Filters: **English, Humans, Adult: 19+ years**	19,671
#3 Exposure, free text	**psychosocial stress*[tiab] OR psychosocial factor*[tiab] OR psychosocial risk*[tiab] OR stress at work[tiab] OR work stress*[tiab] OR occupational stress*[tiab] OR work environment[tiab] OR occupational strain[tiab] OR job characteristic*[tiab] OR job stress*[tiab] OR job strain[tiab] OR job demand*[tiab] OR job control[tiab] OR decision latitude[tiab] OR decision authority[tiab] OR skill discretion[tiab] OR social support[tiab] OR isostrain[tiab] OR workload[tiab] OR time pressure[tiab] OR overtime[tiab] OR hour spent working[tiab] OR emotional demand*[tiab] OR care giver*[tiab] OR social capital[tiab] OR effort-reward imbalance[tiab] OR overcommitment[tiab] OR job insecurity[tiab] OR job security[Tiab] OR downsizing[tiab] OR working hour*[tiab] OR excessive work[tiab] OR sedentary work[tiab] OR violence[tiab] OR bullying[tiab] OR harassment[tiab] OR psychosocial resource*[tiab] OR justice[tiab] OR injustice[tiab] NOT editorial[publication type] NOT letter[publication type] NOT review[publication type] NOT systematic review[publication type]** Filters: **English, Humans, Adult: 19+ years**	99,814
#4 Outcome MeSH	**Myocardial ischemia[Mesh] OR Stroke[Mesh] NOT editorial[publication type] NOT letter[publication type] NOT review[publication type] NOT systematic review[publication type]** Filters: **English, Humans, Adult: 19+ years**	265,693
#5 Outcome, Free text	**heart disease*[ti] OR cardiovascular disease*[tiab] OR cardiovascular event*[ti] OR cardiovascular system[ti] OR cardiovascular outcome*[ti] OR cardiovascular mortality[ti] OR all-cause mortality[ti] OR coronary heart disease*[ti] OR myocardial infarction[tiab] OR coronary event*[ti] OR coronary health[ti] OR stroke[ti] OR cerebrovascular disease*[ti] NOT editorial[publication type] NOT letter[publication type] NOT review[publication type] NOT systematic review[publication type]** Filters: **English, Humans, Adult: 19+ years**	246,260
#6	#2 OR #3 (exposure)	111,183
#7	#4 OR #5 (outcome)	372,122

#8	#6 AND #7 (exposure and outcome)	3893
#9	#8 AND #1 (exposure and outcome and study design)	**2744**

Embase 16.11.2024		
Search	Query	Results
#1 Exposure	('psychosocial stress' or 'psychosocial factor' or 'psychosocial risk' or 'stress at work' or 'work stress' or 'occupational stress' or 'work environment' or 'occupational strain' or 'job characteristic' or 'job stress' or 'job strain' or 'job demand' or 'job control' or 'decision latitude' or 'decision authority' or 'skill discretion' or 'social support' or 'isostrain' or 'workload' or 'time pressure' or 'overtime' or 'hour spent working' or 'emotional demand' or 'care giver' or 'social capital' or 'effort-reward imbalance' or 'overcommitment' or 'job insecurity' or 'job security' or 'downsizing' or 'working hour' or 'excessive work' or 'sedentary work' or 'violence' or 'bullying' or 'harassment' or 'psychosocial resource' or 'justice' or 'injustice').ti,kw	110,819
#2 Outcome	('ischemic hear disease' or 'stroke' or 'heart disease' or 'cardiovascular disease' or 'cardiovascular event' or 'cardiovascular system' or 'cardiovascular outcome' or 'cardiovascular mortality' or 'all-cause mortality' or 'coronary heart disease' or 'myocardial infarction' or 'coronary event' or 'coronary health' or 'cerebrovascular disease').me,ti,ab.	1,987,486
#3 Exposure and outcome	#1 AND #2	2876
#4	limit 3 to (human and English language)	2552
#5	limit 4 to "remove Medline records"	**675**

ANNEX III: Flowchart of literature search



ANNEX IV: Alphabetical list of articles fulfilling in- and exclusion criteria

Alicandro, G., P. Bertuccio, G. Sebastiani, C. La Vecchia and L. Frova (2020). "Long working hours and cardiovascular mortality: a census-based cohort study." Int J Public Health **65**(3): 257-266.

Alterman, T., R. B. Shekelle, S. W. Vernon and K. D. Burau (1994). "Decision latitude, psychologic demand, job strain, and coronary heart disease in the Western Electric Study." Am J Epidemiol **139**(6): 620-627.

André-Petersson, L., G. Engström, B. Hedblad, L. Janzon and M. Rosvall (2007). "Social support at work and the risk of myocardial infarction and stroke in women and men." Soc Sci Med **64**(4): 830-841.

Bonde, J. P., T. Munch-Hansen, E. Agerbo, P. Suadicani, J. Wieclaw and N. Westergaard-Nielsen (2009). "Job strain and ischemic heart disease: a prospective study using a new approach for exposure assessment." J Occup Environ Med **51**(6): 732-738.

De Bacquer, D., E. Pelfrene, E. Clays, R. Mak, M. Moreau, P. de Smet, M. Kornitzer and G. De Backer (2005). "Perceived job stress and incidence of coronary events: 3-year follow-up of the Belgian Job Stress Project cohort." Am J Epidemiol **161**(5): 434-441.

De Vogli, R., J. E. Ferrie, T. Chandola, M. Kivimäki and M. G. Marmot (2007). "Unfairness and health: evidence from the Whitehall II Study." J Epidemiol Community Health **61**(6): 513-518.

Dragano, N., J. Siegrist, S. Nyberg and M. Kivimaki (2017). "Effort-reward imbalance at work and job strain as risk factors for incident coronary heart disease: Results from the multicohort IPD-work consortium." European Journal of Preventive Cardiology **24**(2 Supplement 1): 11.

Eaker, E. D., L. M. Sullivan, M. Kelly-Hayes, R. B. D'Agostino, Sr. and E. J. Benjamin (2004). "Does job strain increase the risk for coronary heart disease or death in men and women? The Framingham Offspring Study." Am J Epidemiol **159**(10): 950-958.

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Ferrie, J. E., M. Kivimäki, M. J. Shipley, G. Davey Smith and M. Virtanen (2013). "Job insecurity and incident coronary heart disease: the Whitehall II prospective cohort study." Atherosclerosis **227**(1): 178-181.

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ANNEX V: Reasons for exclusion of full-text read papers

Main grouping of ineligibility		
	First author, year of publication	Specific reasons for ineligibility
Design issue es		
	Karasek 1982	Some estimates are cross-sectional. Other estimates from case-control studies are not adjusted for socio-economic class.
	Alfredsson 1985	Selective reporting of significant associations only between a large number of JEM based work characteristics and IHD and stroke
	Bobak 1998	Hospital-based case control study with retrospective questionnaire information and IHD diagnoses including non-definite cases
	Hallquist 1998	Hospital-based case control study with retrospective questionnaire information
	Herbert 1998	Cross-sectional study using prevalence data
	Reuterwall 1999	Case control study (SHEEP) with retrospective questionnaire information on psychosocial and other exposures.
	Orth-Gomér 2000	Addresses risk of recurrent CHD in women hospitalized for acute AMI or unstable angina pectoris
	Wamala 2000	Case control study with retrospective questionnaire information on psychosocial and other exposures.
	Sacker 2001	Cross-sectional survey addressing job strain using self-reported, physician diagnosed IHD
	Uchiyama 2005	Study population selected by CVD status (treated hypertension)
	Kopp 2006	Cross-sectional ecologic study design
	Demiral 2006	Cross-sectional study
	Mc Carthy 2012	Case-control study with self-reported exposure data
	Selander 2013	Case-control study (SHEEP) with retrospective questionnaire

		information on psychosocial and other exposures.
	Cheng 2014	Case-control study with retrospective self-reported exposure (average working hours the week before hospital admission for CHD)
	Kang 2014	Cross-sectional study design
	Becher 2018	Self-reported cardiovascular disease: "In the past two years have you consulted a health professional with regard to chest pain, or any other cardiovascular related health problem—such as myocardial infarction, angina, stroke or hypertension? "
	Chen 2018	Outcome and exposure ascertainment insufficiently described. The ICD-10 diagnoses include numerous diagnoses not mentioned. Outcome data partly form database (long working hours), but no details are given. Job strain not defined.
	Fadel 2019	Cross-sectional study with self-reported stroke outcome.
	Magnusson-Hansson 2019	The outcome includes diabetes (cardiometabolic syndrome) and is partly self-reported (in one of five cohorts)
Exposure issues		
	Haynes 1980	No data on the effect of work-related psychosocial exposures.
	Tuchsen 1993	Addresses night and shift work, not long working hours or other workplace psychosocial exposures
	Mathews 2002	Works stress includes a broad range of difficulties related to work (e.g. being fired), and estimates only provided for a number of exposures without specifying which ones.
	De Vogli 2007	Exposure is about 'unfairness' - but about unfair treatment in general and not limited to the workplace which the authors stress explicitly.
	MacLeod 2007	No data on effects of explicit work-related psychosocial exposures.
	Nabi 2008	No analyses on effect of work-related psychosocial exposures.

	Leineweber 2011	No explicit occupational exposure. Is about an individual react to unfairness (coping rather than exposure)
	Kersten 2015	No data on effect of work-related psychosocial exposures.
	Schnohr 2015	No risk estimates adjusted for sex and SES.
	Tillmann 2017	No data on effect of work-related psychosocial exposures Pooling of CVD mortality outcomes (ICD-10 I00-I99).
	Cohen 2019	No data on effects of explicit work-related psychosocial exposures. Composite outcome (pooling of CVD diagnostic subtypes, e.g. AMI and stroke).
	Walli-Attaei 2022	No data on effect of work-related psychosocial exposures
	Santosa 2021	Pool work and non-work questions on stress reactions rather than exposure to psychosocial stressors.
	Ajibewa 2024	Applies a stress score from 5 domains not distinguishing work related stressors
Outcome issues		
	Johnson 1989	Addresses various cardiovascular disorders assembled in one variable: hypertension, ischemic heart disease, cerebrovascular disease and more
	Siegrist 1990	Outcomes include probable coronary heart disease in addition to definite cases
	Siegrist 1992	Outcomes include probable coronary heart disease in addition to definite cases.
	Siegrist 1994	Broadly defined CHD outcome (indefinite or probable CHD).
	Johnson 1996	Addresses various cardiovascular disorders assembled in one variable: ischemic heart disease, cerebrovascular disease and peripheral arterial disease.
	Marmot 1997	Self-reported CHD outcomes
	Bosma 1998	Outcome defined by self-reported angina pectoris or self-reported doctor diagnosed ischemic heart disease.
	Amick 2002	Addresses all-cause mortality, no data on IHD or stroke mortality.

	Kivimaki 2002	CVD mortality outcome includes a range of CVDs in addition to IHD and stroke
	Kivimaki 2003	Uses self-reported CHD data.
	Vahtera 2004	Outcome CVD mortality including the entire I chapter of CVD
	Elovainio 2006	Outcome CVD mortality including the entire I chapter of CVD
	Toivanen 2006	Outcome CVD mortality including pulmonary and peripheral vascular diseases
	Oksanen 2011	Addresses all-cause mortality, no data on IHD or stroke mortality.
	Toker 2012	Self-reported IHD outcomes only partially medically verified
	Szerencsi 2013	Addresses cardiovascular disease without separate analyses of ischemic heart disease or stroke. Self-reported outcome (but medically verified in half of the cohort).
	Nilsen 2016	Addresses all-cause mortality without data on IHD or stroke mortality.
	Marchand 2017	Self-reported heart disease outcome.
	Shin 2017	Case-crossover study with retrospective self-reported exposure (average weekly working hours) during specified time-periods before hospitalisation.
	Kivimaki 2018	Addresses all-cause mortality without separate analyses of ischemic heart disease and stroke.
	Hayashi 2019	IHD outcome include possible not medically verified IHD. The study also reports risk of stroke which is not excluded
	Heslop 2019	CVD mortality is broadly defined (ICD9 390-459) including other CVD than IHD and stroke
	Lee 2019	Self-reported outcome (CVD) without clinical verification.
	Starke 2020	Peripheral disorders are included in the outcome.
	Sørensen 2022	Outcome 'chronic disease' including a range of diseases in addition to CVD.
Analysis issues		

	Alfredsson 1982	Risk estimates are not adjusted for socio-economic position. Case-control study partly with self-reports on psychosocial exposures.
	Alfredsson 1983	Case-control study with partly self-reports on psychosocial exposures.
	Reed 1989	No risk estimates – only age-adjusted CHD incidence rates. No adjustment for socioeconomic class.
	Suadicani 1993	No reporting of adjusted risk estimates.
	Andersen 2004	No adjusted estimates of associations between JEM-based psychosocial exposures and risk of AMI.
	Tenkanen 2005	No risk estimates for work-related psychosocial factors.
	Kornitzer 2006	Risk estimates not controlled for SES.
	Netterstrøm 2006	Insufficient reporting of data analysis. Statistical models with too few details to allow interpretation of provided risk estimates. Analyses by continuous exposure sum scores or dichotomous outcome? Job strain variable in four categories but split values not provided.
	Kivimaki 2008	Risk estimates are not adjusted for SES.
	Ferrario 2011	Risk estimates for psychosocial exposures are not provided.
	Emeny 2013	Case-control study not adjusting for socio-economic position.
	Eriksson 2018	Risk estimates for psychosocial exposures are not provided.
	Framke 2020	Risk estimates for psychosocial exposures are not provided.
	Lee 2021	Risk estimates for long working hours are not provided
	Almroth 2024	Risk estimates for psychosocial exposures are not provided.
Overlapping data		
	Hammar 1994	Data overlapping with Hammar 1994
	Bosma 1997	Data overlapping with Kuper 2002 (Whitehall II)
	Brunner 2004	Overlapping with a more comprehensive report of the same data, Kivimaki 2004

	Kivimaki 2006	Data overlapping with Kuper 2003.
	Tsutsumi 2009	Data overlapping with Tsutsumi 2011
	Kivimaki 2011	Data overlapping with Virtanen 2010.
	Clays 2016	Data overlapping with DeBacker 2005.
	Ferrario 2017	Data overlapping with Ferrario 2019 (same exposure and outcome).
	Magnusson 2020	Same study population as Ferrie 2012 with same risk estimates (besides mediation analyses).
Other issues		
	Aboa-Eboulé 2011	Analyses of recurrent AMI in patients with earlier hospitalisation for AMI.
	Kivimaki 2011	Overlapping with Kuper 2003. Addresses the question whether adding job strain to the Framingham score (hypertension, lipids, smoking, diabetes) improves prediction of CHD.

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ANNEX VI. Descriptive characteristics of papers included in a systematic review of workplace psychosocial exposures and cardiovascular disease

VI-1: JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN

VI-2: EFFORT REWARD IMBALANCE, EFFORT, REWARD

VI-3: JOB INSECURITY, DOWNSIZING, ORGANISATIONAL CHANGE

VI-4: LONG WEEKLY WORKING HOURS

VI-5: OTHER PSYCHOSOCIAL WORKPLACE EXPOSURES

VI-1 JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	COUNTRY	POPULATION	N	WOMEN %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	MINIMALLY ADJUSTED		FULLY ADJUSTED	
					Period	Duration					RR	95% CI	RR	95% CI

FOLLOW-UP STUDIES CARDIOVASCULAR DISEASE

FIRST AUTHOR year (study label)	COUNTRY	POPULATION	N	WOMEN %	Period	Duration	OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	RR	95% CI	RR	95% CI
André-Petersson 2007	Sweden	Residents in Malmø born 1923-1945 invited to a cancer and diet research cohort	7.770	61	1992-2001	8,0	**AMI and stroke** Myocardial Registry based diagnoses for fatal and non-fatal AMI (ICD-9 410, 412) and stroke (ICD-9 430,431,434, 436)	152	Baseline SelfAQ **Isostrain** demands 5 items, decision latitude 6 items, social support 6 items. Job strain, quadrant (split of item scores not provided) Social support a work, split by the mean of item scores. Isostrain low support and high strain vs high support and high strain	Men	nr		0,87	0,60-2,06
										Women	nr		1,42	0,45-4,50
Padyab 2014 (Vaesterbotton intervention Programme, VIP)	Sweden	County residents aged 40, 50 and 60 years of age participating in a health survey at their local primary care center in a Northern Swedish County.	74,988	51	1990-2006	12.0	**CVD mortality** Follow-up in national health registry for death due to myocardial infarction (ICD-10: I21-23, I24, I46) and stroke (ICD-10 I61,I63,I64)	595	Baseline SelfAQ **Job demands** 4 items, 4-point Likert scale. of item values (range 4-16). Sum of item values (range 4-24). Median item scores, high vs low	Men	0.73	0.59-0.89	0.81	0.64-1.03
										Women	0.58	0.39-0.86	0.75	0.47-1.19

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	COUNTRY	POPULATION	N	WOMEN %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	MINIMALLY ADJUSTED		FULLY ADJUSTED	
					Period	Duration					RR	95% CI	RR	95% CI
									Job control 6 items on job decision latitude, 4-point Likert scale. Sum of item values (range 4-24). Median item scores, low vs high	Men	1.37	1.12-1.67	1.07	0.85-1.36
										Women	1.21	0.83-1.76	0.91	0.58-1.43
									Job strain Quadrant, gender-specific median, strain vs relaxed	Men Women	0.87 0.66	0.61-1.24 0.34-1.33	NR	NR
									Isostrain High job strain in combination with low social support from colleagues at work. Dichotomized yes/no	Men Women	1.18 0.51	0.81-1.72 0.21-1.26	NR	NR

FOLLOW-UP STUDIES ISCHEMIC HEART DISEASE

Alterman 1994 (Western Electric Study)	USA	Male middle-aged employees at the Hawthorne Works, Chicago	1,683	0	1957-1983	25.0	**IHD mortality** Death registry	283	JEM survey **Job demands** 10% increase in job-demand item scores	All	0.79	0.48-1.28	0.76	0.55-1.05
									Decision latitude: 20% increase in job control item scores	All	0.76	0.59-0.97	0.85	0.70-1.03

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	**COUNTRY**	**POPULATION**	**N**	**WOMEN %**	**FOLLOW-UP**		**OUTCOME Type Ascertainment**	**N cases**	**EXPOSURE Ascertainment Contrast**	**STRATA**	**MINIMALLY ADJUSTED**		**FULLY ADJUSTED**	
					Period	**Duration**					**RR**	**95% CI**	**RR**	**95% CI**
									Job strain: highest strain vs lowest strain, tertile split	All	1.48	0.98-2.24	1.03	0.75-1.41
Steenland 1997 (NHANES)	USA	Male employees aged 25-74	3,575	0	1971-1987	NR	**IHD** ICD-9 410-414 Hospital discharge diagnoses and death certificates	519	JEM, survey based multi adjusted job scores. Job titles from 1970 US census					
									Job demands: quartiles of item scores, higher vs lowest	**White collar** 2nd quartile			0.69	0.45-1.06
										3rd quartile			1.09	0.73-1.64
										4th quartile			0.93	0.61-1.44
										Blue collar 2nd quartile			0.83	0.62-1.12
										3rdquartile			0.83	0.58-1.18
										4th quartile			0.40	0.64-1.03
									Job control: quartiles of item scores, higher vs lowest	**White collar** 2nd quartile			0.71	0.40-1.28
										3rd quartile			0.97	0.57-1.65
										4thquartile			0.74	0.43-1.26
										Blue collar 2nd quartile			0.87	0.66-1.16
										3rd quartile			0.67	0.48-0.93
										4th quartile			0.69	0.46-1.02
									Job strain, quadrant, median split, strain vs relaxed	White collar			1.05	0.63-1.77

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN													
FIRST AUTHOR year (study label)	**COUNTRY**	**POPULATION**	**N**	**WOMEN %**	**FOLLOW-UP**		**OUTCOME Type Ascertainment**	**N cases**	**EXPOSURE Ascertainment Contrast**	**STRATA**	**MINIMALLY ADJUSTED**		**FULLY ADJUSTED**	
					Period	**Duration**					**RR**	**95% CI**	**RR**	**95% CI**
										Blue collar			1.14	0.80-1.63
Lee 2002 (Nurses Health Study)	USA	Registred nurses in a health study	35,038	100	1992-1996	4.0	**MI and fatal IHD** Review of medical records and death certificates after reported CVD events	146	Baseline selfAQ **Job demands** Tertiles of item scores	Lowest tertile	1	reference	1	reference
										Intermediate tertile	1.35	0.93-1.97	1.32	0.90-1.93
										Highest tertile	0.85	0.55-1.32	0.8	0.52-1.24
									Decision latitude Tertiles of item scores	Highest tertile	1	reference	1	reference
										Intermediate tertile	0.85	0.57-1.28	0.81	0.54-1.22
										Lowest tertile	1.06	0.72-1.58	0.97	0.65-1.45
									Job strain Quadrant, median split, strain vs relaxed	All	0.80	0.48-1.34	0.71	0.42-1.19
									Social support Median split, low vs high	All	1.28	0.90-1.83	1.15	0.80-1.64
Virtanen 2002	Finland	Finish census files including men 25-65 in 1980 with the same occupation 1975 and 1980	Approxi-mately 386.000	0	1981-94	14.0	**MI mortality** National death registry	8,378	JEM expert **Job control** Low vs medium and high (no details)	Men	nr	-	1.11	1.04-1.19
									Work load Medium vs low (no details)	Men	nr	-	1.05	0.97-1.13

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	**COUNTRY**	**POPULATION**	**N**	**WOMEN %**	**FOLLOW-UP**		**OUTCOME Type Ascertainment**	**N cases**	**EXPOSURE Ascertainment Contrast**	**STRATA**	**MINIMALLY ADJUSTED**		**FULLY ADJUSTED**	
					Period	**Duration**					**RR**	**95% CI**	**RR**	**95% CI**
									Work load High vs low	Men	nr	-	1.13	0.96-1.33
Kuper 2003 (Whitehall II)	UK	Civil servants in offices in 20 departments in London	10,308	33	1985-2000	11.0	**MI and fatal IHD** Medical record review of reported events	296	Baseline SelfAQ **Job demands** Tertiles of item scores	**Men** Lowest tertile	1	reference	1	reference
										Intermediate tertile	1.49	1.06-2.10	1.33	0.93-1.90
										Highest tertile	1.22	0.84-1.78	1.17	0.79-1.73
										Women Lowest tertile	1	reference	1	reference
										Intermediate tertile	1.30	0.73-2.30	1.31	0.71-2.40
										Highest tertile	1.37	0.67-2.80	1.85	0.89-3.85
									Decision latitude Tertiles of item scores	**Men** Highest tertile	1	reference	1	reference
										Intermediate tertile	1.32	0.99-1.76	1.32	0.97-1.79
										Lowest tertile	1.14	0.82-1.59	1.01	0.70-1.45
										Women Highest tertile	1	reference	1	reference
										Intermediate tertile	0.68	0.30-1.55	0.70	0.30-1.64
										Lowest Q3	1.06	0.53-2.08	0.92	0.45-0.89
									Job strain Quadrant, median split, strain vs relaxed	All	1.42	0.99-2.05	1.16	0.78-1.71

FIRST AUTHOR year (study label)	COUNTRY	POPULATION	N	WOMEN %	FOLLOW-UP Period	FOLLOW-UP Duration	OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	MINIMALLY ADJUSTED RR	MINIMALLY ADJUSTED 95% CI	FULLY ADJUSTED RR	FULLY ADJUSTED 95% CI
JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
Eaker 2004 (Framingham Offspring Study)	USA	Offspring (and spouses) from a population-based study	3,039	44	1984-99	10.0	**IHD and fatal IHD** Scheduled clinical examinations during follow up, strict criteria. Death certificates	149	Baseline SelfAQ **Job strain** Quadrant, median split, strain vs relaxed (low strain)	Men	NR		1.18	0.69-2.00
										Women	NR		0.61	0.21-1.75
									Job demands Risk by one SD increase in item score	Men	NR		1	0.97-1.04
										Women	NR		0.99	0.93-1.06
									Decision latitude Risk by one SD increase in item score	Men	NR		1	0.95-1.06
										Women	NR		1.85	1.21-2.85
De Bacquer 2005 (BELSTRESS)	Belgium	Employees in 25 large companies and public administrations across Belgium	14,337	0	1994-1999	3.2	**IHD** Medically ascertained acute myocardial infarction, unstable angina, coronary artery bypass or coronary angioplasty at baseline clinical examination	87	Baseline SelfAQ **Job demands**, Tertiles of item scores	Lowest tertile	1	reference	1	reference
										Intermediate tertile	1.14	0.68-1.90	1.26	0.73-2.14
										Highest tertile	1.31	0.77-2.24	1.43	0.80-2.57
									Decision latitude Tertiles of item scores	Highest tertile	1	reference	1	reference
										Intermediate tertile	0.91	0.55-1.52	0.73	0.42-1.26
										Lowest tertile	1	0.60-1.65	0.83	0.48-1.43
									Social support, two subscales, co-worker	Highest tertiles	1	reference	1	reference

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	COUNTRY	POPULATION	N	WOMEN %	FOLLOW-UP Period	Duration	OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	MINIMALLY ADJUSTED RR	95% CI	FULLY ADJUSTED RR	95% CI
									and supervisor support Tertiles of item scores					
										Intermediate tertiles	1.36	0.79-2.32	1.58	0.91-2.74
										Lowest tertiles	2.11	1.27-3.52	2.36	1.38-4.01
									Job strain, quadrant, median split, strain vs relaxed	All	1.35	0.73-2.49	1.26	0.66-2.41
									Isostrain, quadrant, median split, high iso vs low	All	1.91	1.07-3.41	1.92	1.05-3.53
Kuper 2006	Sweden	Women in the Uppsala Health care region enrolled into a cohort study	48,066	100	1991-2002	11.0	**MI and fatal IHD** Registry based medical ascertainment	210	Baseline SelfAQ **Job demands** Tertiles of item scores	Lowest tertile	1	reference	1	Reference
										Intermediate tertile	0.9	0.5-1.6	0.8	0.4-1.5
										Highest tertile	1.4	0.9-2.3	1.4	0.8-2.3
									Decision latitude, Tertiles of item scores	Highest tertile	1	reference	1	reference
										Intermediate tertile	0.8	0.5-1.4	0.8	0.5-1.4
										Lowest tertile	1	0.6-1.6	0.7	0.4-1.2
									Social support, two subscales, co-worker and supervisor support. Tertiles of item scores	Highest tertile	1	reference	1	reference
										Intermediate tertile	0.8	0.5-1.4	1	0.5-1.7

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	COUNTRY	POPULATION	N	WOMEN %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	MINIMALLY ADJUSTED		FULLY ADJUSTED	
					Period	Duration					RR	95% CI	RR	95% CI
										Lowest tertile	1.3	0.8-2.0	1.2	0.7-1.2
									Job strain, quadrant, median split, strain vs relaxed	All	1.4	0.7-2.7	1	0.5-1.9
Bonde 2009	Denmark	A cohort of public service employees at Aarhus County and Aarhus municipality identified from electronic company records	18,258	79	2002-2007	5.0	**IHD** National patient registry, ischemic heart disease ICD-8: 410-414; ICD-10: I21, I22 and I24	101	Workunit, baseline SelfAQ **Job demands** Each employee assigned mean scores of the work unit (1106 work units). Quartiles of work unit average score	Lowest Q4	NR		1	Reference
										Q2 and Q3			1.2	0.7-1.9
										Highest Q1			1.3	0.8-2.3
									Job control Quartiles of work unit average score	Lowest Q4	NR		2	1.1-3.6
										Q2 and Q3			1.4	0.8-2.4
										Highest Q1			1	Reference
									Social support at work Quartiles of work unit average score	Lowest Q4	NR		1.1	0.6-2.0
										Q2 and Q4_3			1	0.6-1.7
										Highest Q1			1	reference
									Job strain Quadrant, median, strain vs all others	All	NR		1.3	0.9-2.1

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	**COUNTRY**	**POPULATION**	**N**	**WOMEN %**	**FOLLOW-UP**		**OUTCOME Type Ascertainment**	**N cases**	**EXPOSURE Ascertainment Contrast**	**STRATA**	**MINIMALLY ADJUSTED**		**FULLY ADJUSTED**	
					Period	**Duration**					**RR**	**95% CI**	**RR**	**95% CI**
Netterstrøm 2010 (Copenhagen City Heart Study)	Denmark	Employed citizens aged 30+ in Copenhagen City	1,141	52	1992-2007	13-15	**IHD or fatal IHD** Patient and death registry, ICD-10 I20-25 or equivalent in ICD-8	IHD 104 MI 49	Baseline SelfAQ 27 items, 3 response categories (often/ sometimes/rarely) **Job demands** High vs low, split unknown	Men	1.1	0.6-1.8	1.5	0.8-2.6
										Women	0.9	0.4-1.8	1.1	0.5-1.3
									Control High vs low, split unknown	Men	0.7	0.4-1.1	0.9	0.5-1.3
										Women	0.6	0.3-1.4	1.2	0.5-3.1
									Social support High vs low, split unknown	Men	0.8	0.5-1.4	0.8	0.5-1.4
										Women	0.6	0.3-1.4	0.9	0.4-1.4
									Job strain Quadrant, split unknown, yes/no	Men	1.3	0.8-2.1	1.6	0.7-3.7
										Women	1.2	0.6-2.3	1.1	0.3-4.2
Kivimaki 2012 (IPD Consortium)	7 European countries	Employees in one of 13 cohorts of the IPD consortium	197,473	49	1985-2006	8.0	**AMI or MI death** Hospital records for admission for non-fatal MI (ICD-10: I21-I22; ICD – 8: 410) or death registries for fatal CHD	2,358	Baseline SelfAQ **Job strain** Quadrant, study specific median, strain vs all other	All	1.23	1.10-1.37	1.17	1.05 -1.31

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	**COUNTRY**	**POPULATION**	**N**	**WOMEN %**	**FOLLOW-UP**		**OUTCOME Type Ascertainment**	**N cases**	**EXPOSURE Ascertainment Contrast**	**STRATA**	**MINIMALLY ADJUSTED**		**FULLY ADJUSTED**	
					Period	**Duration**					**RR**	**95% CI**	**RR**	**95% CI**
Slopen 2012 (Women's Health Study)	USA	Women in health related occupations participating in a study addressing effects of Aspirin	22,086	100	1998-2007	10.0	**IHD or STROKE** Self-reported cases of non-fatal myocardial infarction, coronary revascularisation or ischemic stroke verifed by review of medical records. Fatal CVD, death registry	170	Baseline SelfAQ **Job strain** High demands and low control, quadrant method, median split, high strain vs low strain	MI	1.88	1.18-3.01	1.67	1.04-2.70
								440		Coronary revasc.	1.59	1.19-2.13	1.41	1.05-1.90
								163		Ischemic stroke	1.83	1.12-2.97	1.43	0.87-2.34
Toren 2014	Sweden	Population based cohort in Gotenborg born 1915-1925	6,070	0	1975-2000	16.0	**MI and stroke** Hospital discharge and death registries. Non-fatal MI ICD-10 I21 and ischemic stroke I61-I69. Fatal CHD ICD-10 I20-I25	1,052	JEM survey-based **Job demands** Median split of item scores. High vs low	MI White collar	1.00	0..80-1.26	NR	NR
										MI Blue collar	1.15	0.93-1.41	NR	NR
									Job control Median split of item scores. Low vs high	MI White collar	1.06	0.84-1.33	NR	NR
										MI Blue collar	1.23	0.98-1.56	NR	NR

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	COUNTRY	POPULATION	N	WOMEN %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	MINIMALLY ADJUSTED		FULLY ADJUSTED	
					Period	Duration					RR	95% CI	RR	95% CI
									Job strain Quadrant method, median split, high strain vs relaxed (no strain)	MI White collar	1.15	0.69-1.92	NR	NR
										MI Blue collar	1.36	1.01-1.84	NR	NR
Schiøler 2015	Sweden	A cohort of male construction workers established 1989-93	75,236	0	1989-2004	12.6	**Fatal and non-fatal IHD and ischemic stroke.** Hospitalization for MI (ICD-9 410 or ICD-10 I21 or CHD death (ICD-10 I20-I25) or Ischemic stroke (ICD-10 I63-I64)	CHD 1,884 Stroke 739	Baseline SelfAQ Job content questionnaire using ad hoc questions examined by factor analysis. **Job demands** 4 item scale with 5 response levels. Item scores divided into quintiles; highest vs lowest	MI and IHD death	1.15	0.99-1.33	1.18	1.02-1.37
									Job control 3 items, 5 response levels. Item scores divided into quintiles, lowest vs highest	MI and IHD death	1.12	0.97-129	1.13	0.98-1.31
									Social support 2 items, 5 response scale. Item scores divided into quintiles, lowest vs highest	MI and IHD death	0.98	0.86-1.11	1.01	0.89-1.15
									Job strain: quintiles, quintile split, highest vs lowest	MI and IHD death	1.10	0.89-1.35	1.07	0.87-1.33

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	COUNTRY	POPULATION	N	WOMEN %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	MINIMALLY ADJUSTED		FULLY ADJUSTED	
					Period	Duration					RR	95% CI	RR	95% CI
Ferrario, 2017	Italy	Employees in 3 population-based and one factory-based cohort north of Milan	3,284	0	1989-2008	14.6	**Fatal and non-fatal IHD** Medically verified fatal and non-fatal acute coronary events (AMI, coronary syndrome, revascularization)	172	SelfAQ using modified JCQ. **Job strain** Quadrant, median split, strain vs all others (no strain)	Non-manual workers	NR		1.70	0.94-3.08
										Manual workers	NR		1.94	1.13-3.32
Power, 2019	Canada	Population-based cohort of employed residents 40-60 years old in Quebec recruited through a public health insurance database	8,073	50	2009	6.6	**IHD** Diagnoses from insurance billing system: ICD-9: 410-414 or ICD-10: I21 and I23	557	Baseline SelfAQ **Job strain** JCQ 10-item version. Job strain defined by the ratio of demands and inversed job control item scores. Ratio >= 1.0 vs < 1.0	Men	1.22	0.81-1.84	0.96	0.62-1.49
										Women	1.85	1.19-2.90	1.63	1.02-2.60

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	COUNTRY	POPULATION	N	WOMEN %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	MINIMALLY ADJUSTED		FULLY ADJUSTED	
					Period	Duration					RR	95% CI	RR	95% CI
Niedhammer 2020	France	National representative cohort of employees	1,496,332	47	1976-2002	17.0	**IHD mortality on the job** French national death registry: Deaths ischemic heart disease ICD-10 I20-I25 and equivalent for ICD-8 and 9 Deaths from stroke (ICD-10 I60, I61, I63, I64 and equivalent for ICD-8 and 9)	IHD 1551 Stroke 689	JEM survey Sex, age, job title, industry and companiny size specific JEM based upon occupational JCQ surveys. **Job demands.** Recency weighted cumulative exposure. High psychological demands vs low demands (median split)	IHD mortality on the job Men	NR		1.06	0.92-1.23
										Women			0.92	0.56-1.51
									Decision latitude. Recency weighted cumulative exposure low control vs high control (median split)	IHD mortality on the job Men	NR		1.14	0.98-1.32
										Women			1.26	0.67-2.39
									Social support. Recency weighted cumulative exposure low support vs high support (median split)	IHD mortality on the job Men	NR		1.16	1.00-1.34
										Women			1.58	0.92-2.72
									Job strain. Recency weighted cumulative exposure to low control and high demands vs high control and low demand (median split)	IHD mortality on the job Men	NR		1.16	0.97-1.38
										Women			1.15	0.70-1.89

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	**COUNTRY**	**POPULATION**	**N**	**WOMEN %**	**FOLLOW-UP**		**OUTCOME Type Ascertainment**	**N cases**	**EXPOSURE Ascertainment Contrast**	**STRATA**	**MINIMALLY ADJUSTED**		**FULLY ADJUSTED**	
					Period	**Duration**					**RR**	**95% CI**	**RR**	**95% CI**
									Job isotrain. Recency weighted cumulative exposure to high demands, low control and low support vs low demands, high control and high support	IHD mortality on the job Men	NR--		1.14	0.95-1.37
										Women			1.13	0.68-1.87
Rugulies 2020	Denmark	Employed residents in Denmark 2000	1,660,150	49	2001-2010	10.0	**Fatal and non-fatal MI** National patient registry, myocardial infarction ICD-10 I21 and I22 and CHD mortality (ICD-10 I20-I25)	24,159	JEM survey based. Sex-, age- and calendar year specific JEM assigning work environment survey scores for questions on job demands (3 items) and job control (5 items). **Job strain** quadrant, median splits of item scores, strain vs relaxed	All	1.17	1.14-1.20	1.00	0.98-1.03
Smith 2021	Canada	Employees participating in the nationwide Canadian Community Health Surveys 2000-2003	13,291	48	2001-2017	~15	**MI and congestive heart failure** diagnoses retrieved from two medical databases	641 (calc. from inciden-ce rates)	Baseline interview convenience questions. **Job demands**, 2 items, quartiles of item scores, highest vs lowest	Men	1.05	0.63-1.78	1.10	0.67-1.83
										Women	0.62	0.30-1.28	0.60	0.29-1.24
									Job control, 5 items, quartiles of item scores, lowest vs highest	Men	0.73	0.42-1.27	0.72	0.42-1.24
										Women	0.85	0.46-1.56	0.78	0.42-1.43

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN													
FIRST AUTHOR year (study label)	**COUNTRY**	**POPULATION**	**N**	**WOMEN %**	**FOLLOW-UP**		**OUTCOME Type Ascertainment**	**N cases**	**EXPOSURE Ascertainment Contrast**	**STRATA**	**MINIMALLY ADJUSTED**		**FULLY ADJUSTED**	
					Period	**Duration**					**RR**	**95% CI**	**RR**	**95% CI**
									Job strain quadrant, median split, strain vs no strain (relaxed)	Men	0.83	0.50-1.37	0.82	0.50-1.36
										Women	0.89	0.46-1.73	0.86	0.45-1.65
Wang 2021	USA	Postmenopausal women recruited from 40 clinical centers across USA	80825	100	1993-2013	15.0	**MI and IHD mortality** Medical review of annualy self-reported CHD event for diagnosis of MI and IHD mortality analyzed as a pooled outcome	3,841	JEM based upon independent review of job titles with five items for job demands (different from JCQ) and 8 for job control. **Demand,** median item scores, high vs low	Current workers to retirement	0.90	0.81-0.99	0.96	0.91-1.02
									Control, median item scores, high vs low	Current workers to retirement	0.81	0.74-0.89	0.97	0.92-1.03
									Job strain, quadrant, median splits strain vs relaxed	Current workers to retirement	1.12	0.95-1.32	1.01	0.91-1.10
Lavigne-Robichaud 2023	Canada	White-collar employees in 19 public and semi-public enterprises in the region of Quebec	6,465	52	2000-2018	17.0	**IHD.** Medico-administrative database diagnoses ICD-9: 410-414; ICD-10: I20-I25 (specificity 97.5%)	836	Baseline SelfAQ French version of job content questionnaire (18 items, 4-point Likert scale for demands and control). **Job strain,** quadrant, medium split, strain vs relaxed. Medians based upon general Quebec working population study.	Men Women	1.45 1.08	1.01-2.10 0.65-1.78	1.47 1.02	1.09 -1.99 0.62-1.67

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	**COUNTRY**	**POPULATION**	**N**	**WOMEN %**	**FOLLOW-UP**		**OUTCOME Type Ascertainment**	**N cases**	**EXPOSURE Ascertainment Contrast**	**STRATA**	**MINIMALLY ADJUSTED**		**FULLY ADJUSTED**	
					Period	**Duration**					**RR**	**95% CI**	**RR**	**95% CI**
FOLLOW-UP STUDIES STROKE														
Virtanen 2002	Finland	Finish census files including men 25-65 in 1980 with the same occupation 1975 and 1980	Approxi-mately 386.000	0	1981-94	14.0	**Stroke mortality** National death registry	2,428	JEM expert **Job control** Low vs medium and high (no details)	Men	nr	-	1.19	1.05-1.36
									Workload Medium vs low (no details)	Men	nr	-	1.02	0.89-1.17
									High vs low (no details)	Men	nr	-	1.13	0.84-1.53
Kuper 2007 (Women's Lifestyle and Health cohort)	Sweden	Random sample of women born 1943-62 residing in Uppsala Health care Region	47,942	100	1991-2002	11.0	**Incident stroke** Hospitalization or death from CVD in registries: ischemic stroke (ICD-10 I63.3-I63.9), intracerebral hemorrhage (ICD-10 I61) and undefined stroke (ICD-10 I64) and equivalent earlier ICD versions	200	SelfAQ Job demands, 5 items, control 6 items and social support at work 6 items. **Job demands** Tertiles of item scores, higher vs lowest	**Ischemic stroke** Lowest tertile	1	reference	nr	
										Intermediate tertile	0.8	0.5-1.4		
										Highest tertile	0.9	0.5-1.4		
										Hemorrha-gic stroke Lowest tertile	1	reference	nr	

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	COUNTRY	POPULATION	N	WOMEN %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	MINIMALLY ADJUSTED		FULLY ADJUSTED	
					Period	Duration					RR	95% CI	RR	95% CI
										Intermediate tertile	0.7	0.3-1.7		
										Highest tertile	0.9	0.4-1.9		
									Job control Tertiles of item scores, lower vs highest	**Ischemic stroke** Highest tertile	1	reference	nr	
										Intermediate tertile	0.8	0.4-1.4		
										Lowest tertile	1.4	0.9-2.4		
										Hemorrha-gic stroke Highest tertile	1		nr	
										Intermediate tertile	0.7	0.3-1.6		
										Lowest tertile	1.1	0.5-2.4		
									Social support Tertiles of item scores, lower vs highest	**Ischemic stroke** Highest tertile	1	reference	nr	
										Intermediate tertile	1.1	0.6-1.7		
										Lowest tertile	0.8	0.5-1.3		
										Hemorrha-gic stroke Highest tertile	1	reference	nr	
										Intermediate tertile	1.6	0.7-3.5		
										Lowest tertile	1.1	0.5-2.7		

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	**COUNTRY**	**POPULATION**	**N**	**WOMEN %**	**FOLLOW-UP**		**OUTCOME Type Ascertainment**	**N cases**	**EXPOSURE Ascertainment Contrast**	**STRATA**	**MINIMALLY ADJUSTED**		**FULLY ADJUSTED**	
					Period	**Duration**					**RR**	**95% CI**	**RR**	**95% CI**
									Job strain quadrant, median split, strain vs relaxed	**Ischemic stroke**	1	reference	nr	
										High strain	1.6	0.9-3.0		
										Hemorrha-gic stroke	1	reference		
										High strain	1.2	0.5-3.1		
Kivimaki 2009 (Finnish Public sector Study)	Finland	Personnel in government employment in 10 towns and 21 hospitals	48,361	100	2000-2005	3.0	**Stroke** National Hospital Discharge registry and Statistics Finland Mortality registry: ICD-9: 430-38; ICD-10: I60-I69	124	Baseline SelfAQ Job demands, 3 items and control 9 items with a 5-point Likert scale. Item scores expressed as percentage of max score.	Lowest tertile	1	reference	nr	
									Job demands Tertiles of item scores, higher vs lowest					
										Intermediate tertile	1.4	0.9-2.2		
										Highest tertile	1.9	1.2-3.1		
									Job control Tertiles of item scores, lower vs highest	Lowest tertile	1.03	0.7-1.6	nr	
										Intermediate tertile	1.21	0.8-1.9		
										Highest teetile	1			
									Job strain Quadrant, median split, strain vs relaxed	High strain	1.62	0.9-2.9	nr	

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	COUNTRY	POPULATION	N	WOMEN %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	MINIMALLY ADJUSTED		FULLY ADJUSTED	
					Period	Duration					RR	95% CI	RR	95% CI
Tsutsumi 2011	Japan	Employees <= 65 years old in 12 communities across Japan who participated in routine health screening programs offered to aged people in Japan (response 65%)	6,553	51	1992-2005	11.0	**Stroke** Review of medical records, CT and MR scans in self-reported cases of stroke. Transient ischemic attacks excluded. Cause of deaths retrieved from Cause of death registry.	147	Baseline SelfAQ **Job strain** Quantitative and qualitative job demands (5 items) and control (6 items) with a 4-point Likert scale. Quadrant, sex-specific median split, strain vs relaxed	Men, white collar	nr		1.4	0.3-5.6
										Men, blue collar	nr		3.1	1.0-9.3
										Women, white collar	nr		5.6	1.0-32
										Women, blue collar	nr		1	0.4-2.5
Toren 2014	Sweden	Population based cohort in Gøteborg born 1915-1925	6,070	0	1975-2000	16.0	**Stroke** Hospital discharge and death registries. Non-fatal MI ICD-10 I21 and ischemic stroke I61-I69. Fatal CHD ICD-10 I20-I25	1,052	JEM survey-based **Job demands** Median split of item scores. High vs low	Stroke White collar	0.83	0.62-1.12	NR	NR

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	COUNTRY	POPULATION	N	WOMEN %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	MINIMALLY ADJUSTED		FULLY ADJUSTED	
					Period	Duration					RR	95% CI	RR	95% CI
								549		Stroke Blue collar	1.3	0.97-1.73	NR	NR
									Job control Median split of item scores. Low vs high	Stroke White collar	1.04	0.75-1.40	NR	NR
										Stroke Blue collar	0.96	0.72-1.31	NR	NR
									Job strain Quadrant method, median split, high strain vs relaxed (no strain)	Stroke White collar	0.63	0.29-1.30	NR	NR
										Stroke Blue collar	1.22	0.82-1.82	NR	NR
Fransson 2015 IPD cohort studies	Europe	Employee in European cohort studies, n=14	196,380	53	1985-2008	9.2	**Stroke** Hospital discharge diagnoses and death registries ICD-10 I60-61, I63, I64	1,049	Baseline SelfAQ **Job strain** Quadrant, median split, strain vs all other	All stroke	1.09	0.94-1.26	NR	NR
								476		Ischemic stroke	1.24	1.05-1.47	1.18	1.00-1.39
								2,023		Hemorrhagic stroke	1.01	0.75-1.36	0.95	0.72-1.27

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	COUNTRY	POPULATION	N	WOMEN %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	MINIMALLY ADJUSTED		FULLY ADJUSTED	
					Period	Duration					RR	95% CI	RR	95% CI
Niedhamer 2020	France	National representative cohort of employees	1496332	47	1976-2002	17.0	**Stroke mortality on the job** French national death registry: Deaths ischemic heart disease ICD-10 I20-I25 and equivalent for ICD-8 and 9 Deaths stroke (ICD-10 I60, I61, I63, I64 and equivalent for ICD-8 and 9)	IHD 1,551 Stroke 689	JEM survey Sex, age, job title, industry and company size specific JEM based upon occupational JCQ surveys. **Job demands.** Recency weighted cumulative exposure. High psychological demands vs low demands (median split)	Stroke mortality on the job Men	nr		1.09	0.86-1.40
										Women			1.19	0.82-1.74
									Decision latitude. Recency weighted cumulative exposure low control vs high control (median split)	Stroke mortality on the job Men	nr		1.43	1.11-1.84
										Women			1.61	0.99-2.61
									Social support. Recency weighted cumulative exposure low support vs high support (median split)	Stroke mortality on the job Men	nr		1.07	0.83-1.37
										Women			1.34	0.88-2.04
									Job strain. Recency weighted cumulative exposure to low control and high demands vs high control and low demand (median split)	Stroke mortality on the job Men	nr		1.34	1.01-1.77
										Women			1.59	1.11-2.28

JOB STRAIN, DEMANDS, CONTROL, SOCIAL SUPPORT, ISO STRAIN														
FIRST AUTHOR year (study label)	**COUNTRY**	**POPULATION**	**N**	**WOMEN %**	**FOLLOW-UP**		**OUTCOME Type Ascertainment**	**N cases**	**EXPOSURE Ascertainment Contrast**	**STRATA**	**MINIMALLY ADJUSTED**		**FULLY ADJUSTED**	
					Period	**Duration**					**RR**	**95% CI**	**RR**	**95% CI**
									Job isostrain. Recency weighted cumulative exposure to high demands, low control and low support vs low demands, high control and high support	Stroke mortality on the job Men	nr		1.19	0.88-1.62
										Women			1.62	1.12-2.33

Case-control studies ischemic heart disease

FIRST AUTHOR year (study label)	**COUNTRY**	**POPULATION**	**N**	**WOMEN %**	**Period**	**Duration**	**OUTCOME Type Ascertainment**	**N cases**	**EXPOSURE Ascertainment Contrast**	**STRATA**	**MIN. ADJ. RR**	**MIN. ADJ. 95% CI**	**FULLY ADJ. RR**	**FULLY ADJ. 95% CI**
Hammar 1998	Sweden	Residents in Stockholm County and 4 rural Swedish counties	Cases	10,008	1976-84	11.8	**AMI** Cases of first myocardial infarction through hospital and death registries. Two random controls matched by sex, age and year of coronary event.		JEM based on national occupational interview surveys 1977-1979 linked with census data on job titles.					
			Controls	28,448		12.4			**Job demands** 2 items (hectic and psychologically demanding), median of item scores, high vs low	Men	0.94	0.89-0.99	nr	nr
										Women	0.95	0.82-1.10	nr	nr
									Decision latitude 11 items, median of item scores, low vs high	Men	1.19	1.13-1.25	nr	nr
										Women	1.44	1.25-1.65	nr	nr
									Job strain Quadrant, median split, high vs low	Men	1.21	1.08-1.35	1.12	0.99-1.27
										Women	1.23	1.01-1.51	1.09	0.82-1.44

VI-2 EFFORT REWARD IMBALANCE, EFFORTS AND REWARD

EFFORT REWARD IMBALANCE, EFFORTS AND REWARD														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Minimally adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
Kuper 2002 (Whitehall II)	UK	Civil servants in London offices of 20 departments	10,308	33	1985-2000	11.0	**MI** Clinically verified non-fatal MI based upon self-reports and fatal IHD from death registry	300	Baseline SelfAQ Effort 5 items, rewards 10 items, overcommitment (work stay with you after working hours) 1 item. Items not original ERI questions but have high correlation with these **Effort** Tertiles of item scores	Lowest tertile	1	reference	1	reference
										Intermediate tertile	1.28	0.96-1.71	1.42	1.03-1.95
										Highest tertile	1.08	0.82-1.44	1.28	0.92-1.78
									Reward	Lowest tertile	1.19	1.02-1.38	0.96	0.72-1.28
									Tertiles of item scores	Intermediate tertile	0.99	0.84-1.16	1	0.75-1.34
										Highest tertile	1	reference	1	reference
									Overcommitment Median of item scores	Low	1	reference	1	reference
										High	1.22	0.96-1.54	1.24	0.96-1.60
									Effort reward imbalance Quartiles of ratio of sex specific effort and reward item scores (lowest most favorable)	Q1 (low ERI)	1	reference	1	reference
										Q2	1.23	0.87-1.73	1.44	1.00-2.08
										Q3	1.36	0.97-1.89	1.52	1.06-2.19

EFFORT REWARD IMBALANCE, EFFORTS AND REWARD														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Minimally adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
										Q4 (high ERI)	1.06	0.74-1.51	1.21	0.82-1.78
Dragano 2017 (IPD consortium)	Denmark, Finland, France, Germany, Sweden, UK	Employees from 11 national samples, from public administration and service and from private manufacturing and other companies	90,164	55	1985-2005	8.0	**MI and fatal IHD** Hospital records for admission for non-fatal myocardial infacrtion or death registries for fatal IHD (ICD-10 I21-I22; ICD - 8 410)	1,078	Baseline SelfAQ **Effort reward imbalance** Harmonized scale based upon abbreviated versions of the original ERI scale used in the different cohorts. **Effort** Median item score, high vs low	All	0.99	0.87-1.13	nr	
									Reward Median item score, low vs high	All	1.18	1.04-1.33	nr	
									Effort-reward imbalance Dichotomisation of the ratio of the harmonized effort and reward scale: > 1.0 vs <= 1.0	All	1.16	1.01-1.34	1.16	1.00-1.35
Wu 2019	Taiwan	Professional bus drivers recruited form a large bus company	1,650	0	2006-2012	7.0	**IHD and stroke** National Health Insurance research database: IHD ICD9-CM 410-14; CVD ICD9-CM 430-438	18	Baseline selfAQ **Overcommitment** 6 items Continuous item scores, higher score higher commitment	IHD	1.27	1.04-1.56	1.32	1.05-1.65
								7		Stroke	0.89	0.54-1.46	nr	nr

EFFORT REWARD IMBALANCE, EFFORTS AND REWARD														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Minimally adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
Lavigne-Robichaud 2023	Canada	White-collar employees in 19 public and semi-public enterprises in Quebec region	6,465	52	2000-2018	17.0	**IHD.** Medico-administrative databases diagnoses ICD-9: 410-414; ICD-10: I20-I25 (specificity 97.5%)	836	Baseline SelfAQ Effort-reward ratio. Effort and reward each measured by 9-items, on a 4-point Likert scale. Item score used to define effort/reward ratio dichotomized, split level 25%/75% (our calculation). High effort-reward ratio vs low	Men	1.5	1.23-1.81	1.55	1.26-1.90
										Women	1.08	0.78-1.48	1.02	0.72-1.44

ANNEX VI-3 JOB INSECURITY, DOWNSIZING AND ORGANISATIONAL CHANGE

JOB INSECURITY, DOWNSIZING AND ORGANISATIONAL CHANGE														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Minimally adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
FOLLOW-UP STUDIES JOB INSECURITY														
Lee 2004 (Nurses' Health Study)	USA	Registered nurses 30-55 years old in 1976	36,910	100	1992-1996	4.0	**MI and fatal IHD.** Medical record review of reported events	154	**Job insecurity** 4 items, binary response categories. Worries about unemployment, job transfer, become superfluous, difficulties finding a new job. No data on scale	Follow-up 1992-94	1.47	0.95-2.53	1.35	0.78-2.34
										Follow-up 1992-96	1.14	0.69-1.57	1.04	0.69-1.57

JOB INSUSECURITY, DOWNSIZING AND ORGANISATIONAL CHANGE														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Minimally adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
Netterstrøm 2010 (Copenhagen City Heart Study)	Denmark	Employed citizens age 30+ in Copenhagen City	1,141	52	1992-2007	13-15	**IHD or fatal IHD** Patient and death registry, ICD-10 I20-25 or equivalent in ICD-8	IHD 104 MI 49	**Job insecurity** 4 items, binary response categories. Worries about unemployment, job transfer, become superfluous, difficulties finding a new job. High vs low (unspecified)	Men	2.1	1.2-3.6	2.5	1.1-5.6
										Women	1.6	07-3.4	1.4	0.5-3.2
Slopen 2012 (Women's Health Study)	USA	Women in health-related occupations participating in a RCT across USA addressing effect of aspirin	22,086	100	1998-2007	10.0	**IHD or STROKE** Self-reported cases of non-fatal myocardial infarction, coronary revascularization or ischemic stroke verified by review of medical records. Fatal CVD, registry	170	Baseline SelfAQ **Job insecurity** 1 item, 4 response categories: 'My job security is good' (strongly disagree, strongly agree) Strongly disagree or disagree on good job security vs all other	Myocardial infarction	1.39	0.98-1.97	1.35	0.95 - 1.92
								440		Coronary revasculariza tion	1.22	0.97-1.53	1.19	0.95 - 1.49
								163		Ischemic stroke	0.97	0.65-1.45	0.94	0.63-1.40
Ferrie 2013 (Whitehall II)	UK	Civil servants	4,174	30	1995-2004	8.6	**Fatal and non-fatal IHD** Self-reported data non-fatal and fatal coronary heart disease (inclding angina) verified by medical records and death certificates	168	Baseline SelfAQ **Job insecurity** 1 item, 4 response categories: How secure is your present job? Very insecure or insecure versus secure or very secure	All	1.42	1.05-1.93	1.26	0.91-1.73

JOB INSECURITY, DOWNSIZING AND ORGANISATIONAL CHANGE															
First author year (study label)	**Country**	**Population**	**N**	**Women, %**	**FOLLOW-UP**		**OUTCOME Type Ascertainment**	**N cases**	**EXPOSURE Ascertainment Contrast**	**STRATA**	**Minimally adjusted**		**Fully adjusted**	
					Period	**Duration**					**RR**	**95% CI**	**RR**	**95% CI**
Virtanen 2013 (IPD Consortium Study)	Belgium, Denmark, Germany, Finland, Sweden	12 cohorts of employees from national random samples, from public administration and service and from private manufacturing and other companies	109,257	55	1980s->2004	9.0	**MI and fatal IHD.** Hospital records for admission for non-fatal myocardial infarction (ICD-10 I21-I22 or equivalent) or death registries for fatal coronary heart disease (ICD-10 I20-I25 or equivalent	1,346	Baseline SelfAQ **Job insecurity** 1-2 items, 2-5 response categories about perceived insecurity in current employment. Perceived insecurity yes/no	All	nr		1.05	0.90-1.24
Latza 2015	Denmark	Random sample of employees from the Danish Work Environment Cohort Study	12,559	52	1990-2010	<40-70+	**Fatal and non-fatal IHD** First-time hospital discharge or mortality diagnoses ICD-10 I20-25 or equivalent	561	Baseline SelfAQ **Job insecurity** 2 items, 'Worried about becoming unemployed:; 'difficulties finding a new job'; Worried and/or difficulties, yes vs no	All	1.23	0.98-1.55	1.19	0.94-1.51
REGISTERBASED STUDIES OF DOWNSIZING OR ORGANISATIONAL CHANGE															

JOB INSECURITY, DOWNSIZING AND ORGANISATIONAL CHANGE														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Minimally adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
Martikainen, 2008	Finland	Random sample of employees living i Finland with oversampling of deaths and downsized workplaces	85,833	41	1995-2002	8.0	**IHD mortality** Finnish death registry (ischemic heart disease, no ICD-10 codes provided)	1,188	Registry linkages **Downsizing** Remaining in downsized workplaces vs workplaces with no downsizing during a period based upon registry linkages	< 9%	nd		1	reference
										10-29%	nd		0.9	0.73-1.12
										30-49%	nd		1.11	0.77-1.61
										50-100%	nd		0.78	0.52-1.17
Jensen 2020 (WHALE)	Denmark	Municipal employees in the capital region who in 2013 worked in the same work unit with > 3 members	14.788	77	2014	1,0	**Fatal and non-fatal IHD or stroke)** First-time hospital discharge or death from ischemic heart disease (ICD-10: I20-I25) or stroke (ICD-10: I61, I63-64)	72	Manager questionnaire **Work unit organizational change.** Email survey addressing lowest-level managers of work units asking about specific organizational change during 2013, yes vs no.	Merge of departments or units	0.94	0.44-2.01	1.24	0.58-2.71
										Split-ups	0.76	0.23-2.55	0.84	0.25-2.82
										Relocation	1.01	0.43-2.36	1.4	0.56-3.51
										Change in manage-ment	1.56	0.87-2.78	1.99	1.07-3.69
										Employee layoff	1.89	1.08-3.29	2.36	1.25-4.47
										Budget cuts	0.88	0.41-1.90	0.86	0.38-1.92

ANNEX VI-4 LONG WEEKLY WORKING HOURS

LONG WEEKLY WORKING HOURS														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Age and sex adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
ISCHEMIC HEART DISEASE														
Holtermann 2010	Denmark	Employees at 14 private and public companies in Copenhagen	4,943	0	1970-2001	30.0	**IHD mortality** National death registry ICD-8 410-414, ICD-10 I20-I25	587	Baseline interview, weekly working hours stratified by physical fitness, Reference <= 40 hours/week	Lowest physical Fitness quintile 41-45 h/w	1.94	1.02-3.72	1.49	0.76-2.89
										46+ h/w	2.69	1.33-5.46	2.28	1.10-4.73
										Three intermediate physical fitness quintiles 41-45 h/w	1.71	1.18-2.49	1.37	0.93-2.03
										46+ h/w	1.06	0.67-1.66	0.94	0.59-1.51
										Highest physical fitness quintile 41-45 h/w	0.98	0.52-1.82	0.8	0.41-1.57
										46+ w/h	0.87	0.41-1.87	0.91	0.41-2.02

LONG WEEKLY WORKING HOURS														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Age and sex adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
Virtanen 2010 (Whitehall II)	UK	Civil servants in London offices in 20 departments	6,014	29	1991-2004	11.0	**MI** Clinically verified fatal and non-fatal MI	159	Baseline AQ. **Working overtime** Single item on an average weekday: Approximately how many hours do you spend on the following activities (if applicable): Work (daytime) and work brought home (hours/w)	No overtime	1	reference	1	reference
										1 hour overtime	0.95	0.61-1.49	0.93	0.59-1.47
										2 hours overtime	1.46	0.93-2.30	1.26	0.79-2.02
										3-4 hours overtime	1.9	1.17-3.06	1.67	1.02-2.76

LONG WEEKLY WORKING HOURS															
First author year (study label)	**Country**	**Population**	**N**	**Women, %**	**FOLLOW-UP**		**OUTCOME Type Ascertainment**	**N cases**	**EXPOSURE Ascertainment Contrast**	**STRATA**	**Age and sex adjusted**		**Fully adjusted**	
					Period	**Duration**					**RR**	**95% CI**	**RR**	**95% CI**
O'Reilly 2013 (NIMS)	Northern Ireland	2001 census cohort of men and women in full-time employ-ment aged 20 - 59/64 years	414,949	35	2001-2009	9.0	**IHD mortality** Cause-specific mortality due to ischemic heart disease (ICD-10 I20-I25)	957	Census questionnaire data **Long working hours** How many hours a week do you usually work in your main job past 4 weeks. Exposure dichotomized: >55 h/w vs 35-40 h/w	**Men** Managerial/professional	nr		0.82	0.55-1.23
										Intermediate			0.36	0.05-2.61
										Own account			1.24	0.88-1.74
										Routine occupations			1.53	1.08-2.17
										Women				
										Managerial/professional	nr		1.25	0.16-9.43
										Intermediate			nr	
										Own account			1.35	0.77-23.9
										Routine occupations			1.93	0.44-8.47

LONG WEEKLY WORKING HOURS														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Age and sex adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
Kivimaki 2015 (1) (IPD consortium)	Europe	European cohorts with unpublished individual participant data, n=10	11,044	0-80	1992-2006	nr	IHD National health registries	812	Baseline SelfAQ **Weekly working hours**, above 55 Hours/week vs < 35-40 hours/week	> 55 h/w	0.87	0.68-1.12	nr	
Hannerz 2018a	Denmark	Random population sample of 20–64-year-old full-time employees (Danish labour force surveys)	145,861	47	1999-2013	8.0	**Fatal and non-fatal IHD** Hospital discharge diagnosis or death registry ICD-10: I20-I25)	3,635	Telephone interview **Long working hours** Number of hours usually worked in a week and in a specific reference week 1–4 weeks prior to the interview. Average weekly working hours h/w	32-40 h/w	nr		1	reference
										41-48 h/w	nr		0.95	0.85-1.06
										>48 h/w	nr		1.07	0.94-1.21
Alicandro 2020	Italy	2011 Italian census, workers 20-64 years old	11,903,540	32	2011-2016	5.0	**IHD mortality** Death registries, ICD-10 I20-25	IHD 7,954	Census data **Long working hours** Number of hours usually worked per week at baseline. Reference is <= 40 h/w	**Men** 41-48	0.91	0.85-0.97	0.91	0.85-0.97
										49-54	0.86	0.78-0.93	0.91	0.83-1.00
										>=55	0.91	0.83-1.00	0.95	0.86-1.00
										Women 41-48	0.93	0.71-1.22	0.86	0.65-1.14
										49-54	0.96	0.65-1.42	0.92	0.61-1.37
										>=55	1.28	0.88-1.87	1.18	0.79-1.76

LONG WEEKLY WORKING HOURS														
First author year (study label)	**Country**	**Population**	**N**	**Women, %**	**FOLLOW-UP**		**OUTCOME Type Ascertainment**	**N cases**	**EXPOSURE Ascertainment Contrast**	**STRATA**	**Age and sex adjusted**		**Fully adjusted**	
					Period	**Duration**					**RR**	**95% CI**	**RR**	**95% CI**
STROKE														
O'Reilly 2013 (NIMS)	Northern Ireland	2001 census cohort of men and women in full-time employment aged 20 - 59/64 years	414,949	35	2001-2009	9.0	**Stroke mortality** Cause-specific mortality due to stroke (ICD-10 I60-69) retrieved from death registry	215	Census questionnaire data **Long working hours** How many hours a week do you usually work in your main job past 4 weeks. Exposure dichotomized: >55 h/w vs 35-40 h/w	**Men** Managerial/professional	nr		1.43	0.51-3.97
										Intermediate			nr	
										Own account			0.52	0.23-1.20
										Routine occupations			2.65	1.28-5.50
										Women				
										Managerial/professional	nr		1.07	0.14-8.0
										Intermediate			nr	
										Own account			2.98	0.48-18.5
										Routine occupations			nr	
Kivimaki 2015 (2) (IPD consortium)	Europe	European cohorts with unpublished individual participant data, n=6	77,168	43-56	1992-2006	nr	**Stroke** National health registries	659	Baseline SelfAQ **Weekly working hours** Reference 35-40 hours/week	>40-48 h/w	1.37	1.05-1.79	nr	
										>48-55 h/w	1.07	0.86-1.33	nr	

LONG WEEKLY WORKING HOURS														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Age and sex adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
										> 55 h/w	1.28	0.99-1.65	nr	
Hannerz 2018 b	Denmark	Random population sample of 20-64 year old full-time employees (Danish labour force surveys)	199,035	52	1999-2013	8.0	**Fatal and non-fatal stroke** Hospital discharge diagnosis or death registry ICD-10: I60, I61, I63, I64)	2,184	Telephone interview **Long working hours** Number of hours usually worked in a week and in a specific reference week 1–4 weeks prior to the interview. Average weekly working hours h/w	**Stroke overall** <35 h/w	nr		0.97	0.87-1.09
										35-40 h/w			1	reference
										41-48 h/w			0.97	0.83-1.13
										49-54 h/w			1.1	0.86-1.39
										> 55 h/w			0.89	0.69-1.16
										Ischemic stroke <35 h/w	nr		1.16	1.00-1.34
										35-40 h/w			1	reference
										41-48 h/w			1.01	0.83-1.23
										49-54 h/w			0.85	0.60-1.22
										> 55 h/w			0.86	0.61-1.22
										Hemorrhagic stroke <35 h/w			0.82	0.64-1.04

LONG WEEKLY WORKING HOURS														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Age and sex adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
										35-40 h/w	nr		1	reference
										41-48 h/w			1.1	0.81-1.50
										49-54 h/w			1.58	1.01-2.46
										> 55 h/w			1.33	0.82-2.15
Hayashi 2019	Japan	Residents of 5 public health center areas, age 40-69 at baseline (82.7% response rate)	15,277	0	1993-2012	20.0	**Stroke** Medically verified stroke according to hospital medical records	439	Baseline SelfAQ **Long Working hours** number of hours worked per day (baseline) or ticking one of 5 categories (< 7 h/d ... >= 11 h/d (10 year follow-up survey). Average working hours per day (unspecified)	**Ischemic stroke** < 35 h/w	1.15	0.90-1.48	1	0.73-1.37
										35-<45 h/w	1	reference	1	reference
										45-<55 h/w	0.98	0.76-1.25	0.96	0.73-1.26
										55+ h/w	0.98	0.69-1.41	0.95	0.64-1.41
								303		**Hemorrhagic stroke** < 35 h/w	1.06	0.77-1.46	1.07	0.73-1.56
										35-<45 h/w	1	reference	1	reference
										45-<55 h/w	1.14	0.86-1.50	1.2	0.89-1.62
										55+ h/w	0.72	0.45-1.15	0.64	0.37-1.09

LONG WEEKLY WORKING HOURS														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Age and sex adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
Alicandro 2020	Italy	2011 Italian census, workers 20-64 years old	11,903,540	32	2011-2016	5.0	**STROKE mortality** Death registries, stroke I60-I69	CVD 2,651	Census data **Long working hours** Number of hours usually worked per week at baseline. Reference is <= 40 h/w	**Men** 41-48	1.05	0.93-1.18	1.05	0.93-1.18
										49-54	0.84	0.71-1.00	0.93	0.78-1.10
										>=55	0.9	0.75-1.08	0.95	0.79-1.15
										Women 41-48	1.04	0.81-1.34	1.02	0.79-1.32
										49-54	0.96	0.65-1.40	0.99	0.67-1.46
										>=55	0.96	0.63-1.47	0.98	0.62-1.53

CASE-CONTROL STUDIES

Sokejima 1998	Japan	Patients admitted to three hospitals for first-time AMI	Cases	526	1990-93	na	**AMI** Clinical criteria AMI (chest pain, ECD, enzymes)	195	Selfreported mean working hours/day preceding month assisted by salary tables (recalculated hours/week)	<=35	3.07	1.77-5.32	2.83	1.52-5.28
										>35-45	1	reference	1	Reference
										>45-55	1.06	0.68-1.67	0.96	0.58-1.60
										>55	2.94	1.26-4.73	2.94	1.39-6.25

ANNEX VI-5 OTHER PSYCHOSOCIAL EXPOSURES

OTHER PSYCHOSOCIAL EXPOSURES														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Age and sex adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
BULLYING AND VIOLENCE														
Xu 2019	Denmark, Sweden	Employed members of 4 occupational cohorts	79,201	53	1995-2011	12.4	**AMI and stroke** Hospital discharge and death registries Myocardial infarction (ICD-8 or ICD-9: 410, ICD-10 I21-I22) or CHD death. Ischemic stroke (ICD-8 or ICD-9: 433-34, ICD-10 I63) Hemorrhagic stroke (ICD-8 or ICD-9: 431, ICD-10 I63-I62)	IHD 484 stroke 301	Baseline SelfAQ **Bullying and violence** Being bullied or exposed to violence or threats of violence past 12 months prior to baseline regardless of frequency Bullying yes vs no	Myocardial infarction	nr		1.21	0.83-1.77
										Hemorrha-gic stroke	nr		2.73	1.16-6.45
										Ischemic stroke	nr		1.44	0.93-2.23
									Violence or threats of violence yes vs no	Myocardial infarction	nr		1.15	1.06-1.49
										Hemorrha-gic stroke	nr		1.31	0.89-1.92

OTHER PSYCHOSOCIAL EXPOSURES														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Age and sex adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
										Ischemic stroke	nr		1.33	1.08-1.64
KC 2024	Sweden	Female employees participating in the Swedish Work environment Surveys 1995-2015	88,904	52	1995-2015	11.0	**IHD and stroke** Incident cases of IHD (ICD-10 I20.0, I20.1, I21-I25) and CBD (ICD-10 I60-69) identified in national hospital patient and death registry	4,218	Baseline SelfAQ **Sexual harassment** Perception of being subject to sexual harassment past 12 months at the workplace with 7-point Likert response scale (never,.. ,daily). Perception of sexual harassment at work past 12 months regardless of frequency vs never exposed	IHD	1.26	0.99-1.91	1.24	0.97-1.59
										Myocardial infarction	1.29	0.95-1.75	1.26	0.92-1.71
										Stroke	1.11	0.80-1.55	1.08	0.77-1.51
PREDICTABILITY														
Vaananen 2008 (Still Working Study)	Finland	A cohort of blue- and white-collar employees at a multinational forest industry	7,663	22	1987-2004	17.0	**AMI** Hospital discharge and death registries, (No ICD codes provided)	372	Baseline SelfAQ **Predictability**, 1 SD decrease of item score	All			1.13	1.01-1.26

ORGANISATIONAL JUSTICE

OTHER PSYCHOSOCIAL EXPOSURES														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Age and sex adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
Kivimaki 2005 (Whitehall II)	UK	Civil servants in London offices of 20 departments	6,128	0	1985-1999	8.7	**IHD** Review of medical information in self-reported cases and death registry. AMI and definite angina ICD-9: 410-414	250	SelfAQ **Relational justice** 5 items, Likert scale tertiles of average item scores phase 1 and 2.	Lowest tertile (low justice)	1	reference	1	reference
										Intermedi-ate tertile	1.05	0.78-1.41	1.12	0.83-1.51
										Highest tertile (high justice)	0.65	0.47-0.91	0.71	0.51-0.99
JOB SATISFACTION														
Netterstrøm 2010 (Copenhagen City Heart Study)	Denmark	Employed citizens age 30+ in Copenhagen City	1,141	52	1992-2007	13-15	**IHD or fatal IHD** Patient and death registry, ICD-10 I20-25 or equivalent in ICD-8	IHD 104 MI 49	SelfAQ **Job satisfaction,** High vs low, split unknown	Men	2.1	1.2-3.6	2.5	1.1-5.6
										Women	1.6	07-3.4	1.4	0.5-3.2
OTHER PSYCHOSOCIAL EXPOSURES														

OTHER PSYCHOSOCIAL EXPOSURES														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Age and sex adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
Theorell 1977	Sweden	Building construction workers in Stockholm	5,187	0	1972-74	2.0	**MI** Hospital discharge diagnoses and death registry	51	Baseline SelfAQ, **Workload** Factor analysis of 60 psychosocial items resulting in one work-related cluster of 12 items labeled 'workload'. Workload, yes vs no	Men	2.03	1.12-3.57		
Lynch 1997 (Kupio IHD Risk Factor Study)	Finland	Population-based sample of male residents in the town of Kuopio and its surrounding communities	1,727	0	1984-1992	6.0	**MI (non-fatal and IHD death)** WHO MONICA AMI registry	89	Baseline SelfAQ **Demands, resources and income** Mental strain due to combinations of demanding work (median split), resources (median split) and income (60/40% split)	**High income:** High/low/high vs low/high/high	0.67	0.29-1.57	0.5	0.21-1.20
										Low income High/low/low vs low/high/high	2.59	1.36-4.94	1.57	0.78-3.18

OTHER PSYCHOSOCIAL EXPOSURES														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Age and sex adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
Xu 2022 (WEHD, FPS, SLOSH)	Denmark, Finland, Sweden	Three population-based cohort studies including employees in public and private companies	135,669	65	2000-2016	7.0	**IHD and stroke** Incident cases of IHD (ICD-10 I20.0, I20.1, I21-I25) and stroke (ICD-10 I60-69) identified in national hospital patient and death registries	CVD 2,190	Baseline SelfAQ **Workplace resources** Latent class analysis of perceived workplace collaboration, support, leadership and procedural justice resulting in different levels of horizontal and vertical workplace resources. Three levels of horizontal and vertical resources, respectively. High horizontal and vertical resources vs low horizontal and vertical resources	Overall CVD	nr	nr	0.92	0.77-1.10
								IHD 1,175		MI	nr	nr	0.88	0.70-1.09
								Stroke 1,097		Ischemic stroke	nr	nr	0.91	0.72-1.15
										Hemorrha-gic stroke	nr	nr	0.58	0.35-0.96
Hibbard 1993 (HMO survey)	USA	Randomly selected participants in household interview surveys 1970-71	2,157	54	1970-85	15.0	**IHD (ICDA-9 410-14) and stroke (ICDA 430-38)** Medical records and death registry	nr	Baseline interview, **Work stress**, item scores 10-26, continuous, higher exposure with increasing item score	**IHD** Men	nr		1.1	1.0-1.2
								nr		Women	nr		1	0.8-1.3

OTHER PSYCHOSOCIAL EXPOSURES														
First author year (study label)	Country	Population	N	Women, %	FOLLOW-UP		OUTCOME Type Ascertainment	N cases	EXPOSURE Ascertainment Contrast	STRATA	Age and sex adjusted		Fully adjusted	
					Period	Duration					RR	95% CI	RR	95% CI
										Stroke Men	nr		1	0.9-1.1
										Women	nr		0.9	0.7-1.1
									Work satisfaction, item scores 10-30, continuous, higher satisfaction with increasing item score	**IHD** Men	nr		1	0.9-1.0
										Women	nr		1.1	0.9-1.3
										Stroke Men	nr		1	0.9-1.1
										Women	nr		1.1	0.9-1.3
Allesøe 2010	Denmark	Danish nurses	12,116	100	1994-2008	15.0	**IHD** Patient registry, ICD-10 I20-25 or equivalent in ICD-8	580	SelfAQ **Work pressure/work speed**, 2 items	A little too high	1.25	1.04-1.50	1.26	1.03-1.53
										Much too high	1.47	1.14-1.88	1.38	1.04-1.81
									Influence daily work, 1 item	Some influence	1.02	0.86-1.22		
										Minor influence	1.01	0.76-1.34		

ANNEX VII: Examples of typically used items in epidemiological studies of the demand-control-support and the effort-reward imbalance models.

Demand-control-support model (The original full Job Content Questionnaire (JCQ), [132]. Many studies use a selection and/or adaptions of items.	
Dimension	Items
Psychological demands	
	My job requires working very hard.
	I am not asked to do an excessive amount of work. *(reverse)*
	I have enough time to get the job done.
	I am free from conflicting demands that others make. *(reverse conflict)*
	My job requires working very fast.
	I have to work intensely.
	I have to concentrate a great deal.
	I do not experience mental overload. *(reverse)*
	I am helped by chance interruptions that I do not cause. *(reverse interruptions)*
Decision authority (part of decision latitude)	
	I have a lot of say about what goes on in my job
	My job allows me to make quite a few decisions on my own
	I have the freedom to decide how I do my job
Skill descrition (part of decison latitude)	
	My job requires that I learn new things
	My job is complex
	I get to do a lot of creative work
	My job allows me to make a lot of decisions on my own
	My job allows me to develop my own special abilities
	My job requires a high level of skill
	People I work with are helpful in getting the job done
	My supervisor is helpful in getting the job done
Social support (up to 8 items)	
Coworker support	People I work with are friendly.
	People I work with are helpful.
	People I work with are willing to listen to my work-related problems.
	People I work with are good at resolving conflicts.
Supervisor support	My supervisor is helpful in getting the job done.
	My supervisor is good at resolving conflicts.
	My supervisor is interested in the feelings of those under them.
	My supervisor pays attention to what I am saying.
Items are typically responded to using 4 to 5-point Likert scales (e.g., 1 = “strongly disagree” to 4 = “strongly agree”) and values for each dimension defined by summing of item-response values.	

Effort-reward imbalance model [84]. Most studies use a selection and/or adaption of items.	
Dimension	Items
Extrinsic efforts	
	I have constant time pressure due to a heavy workload
	I am under constant pressure in my job
	I have to work very hard
	My job is physically demanding
	I have a lot of responsibility in my job
	I am frequently interrupted in my job (e.g. by others or phonecalls).
Reward	
Esteem	I receive the respect I deserve from my superior or a relevant person
	I receive the respect I deserve from my colleagues
Salary/promotion	My job promotion prospects are poor
	My job security is poor
Career development	I have little chance for advancement
	The prospects of job promotion are poor
Overcommitment	
	As soon as I get up in the morning, I start thinking about work problems
	When I get home, I can easily switch off work mentally *(reverse scored)*
	People close to me say I sacrifice too much for my job
	I start working even during my leisure time
	If I postpone something, I feel uneasy until it's done
	Once I get going on a task, I cannot easily stop until it's done
Items are typically responded to using 4 to 5-point Likert scales (e.g., 1 = "strongly disagree" to 4 = "strongly agree") and values for each dimension defined by summing of item-response values. Effort-reward imbalance is typically defined by the ratio: Effort / Reward where sum values are corrected by a factor for item count	

ANNEX VIII: List of included diagnoses.

ICD-8 and 9:

Ischemic Heart Disease: 410–414

410 Acute myocardial infarction

411 Other acute and subacute forms of ischemic heart disease

412 Old myocardial infarction

413 Angina pectoris

414 Other forms of chronic ischemic heart disease

Cerebrovascular Disease: 430–434, 436

430 Subarachnoid haemorrhage

431 Intracerebral haemorrhage

432 Other and unspecified intracranial hemorrhage

433 Occlusion and stenosis of precerebral arteries

434 Occlusion of cerebral arteries

436 Acute but ill-defined cerebrovascular disease

ICD-10

Ischemic Heart Disease: I20–I25

I20 Angina pectoris

I21 Acute myocardial infarction

I22 Subsequent myocardial infarction

I23 Certain current complications following acute myocardial infarction

I24 Other acute ischemic heart diseases

I25 Chronic ischemic heart disease

Cerebrovascular Disease: I61–I65

I61 Intracerebral haemorrhage

I62 Other nontraumatic intracranial haemorrhage

I63 Cerebral infarction

I64 Stroke, not specified as haemorrhage or infarction

I65 Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction

ANNEX IX. External reviews with author responses.

Review by professor Bengt Järvholm, University of Umeå, Umeå, Sweden, 3.9.2025.

Thank you for letting me review the report about "the risk of ischemic heart disease and stroke according to a range of work-related psychosocial exposures: a systematic review with meta-analyses"

This report was commissioned to "review the correlation between exposure to mental stress in the working environment and the development of cardiovascular disease" according to the foreword. The review follows the outlines of a methodology often used in recent Cochrane reviews on associations between occupational exposure and diseases. The review focuses on some exposure models to mental stress as

- Demand-control-support
- Effort – reward imbalance
- Job insecurity
- Long weekly working hours
- Other exposures as
  - Workplace resources
  - Bullying and violence
  - Workplace sexual harassment
  - Predictability on the job
  - Job satisfaction and dissatisfaction
  - Work pressure/speed
  - Psychological demands and resources

The selection of studies to review, the analysis of their findings and presentations are very well performed and clear.

Reviewer

I miss a discussion of mechanisms. Why do these "mental exposures" cause cardiovascular diseases? Some aspects to discuss are[1]

- Are the effects mainly or partially through effects on CNS and/or autonomic neural systems?

- Is the effect an increased occurrence of atherosclerosis?

- Will exposures lead to behavioral changes, e.g. make smokers smoke more or that non-smokers start to smoke? Some smokers say that smoking is nice since it gets you calmer.

- Is the effect dependent on long term (months/years) of exposure or through short term (trigger) effects.

I think that conclusions about a causal association always need a discussion about mechanisms. Absence of reasonable mechanisms decreases the evidence of a causal association.

1 (e.g. Stepotoe &Kivimäki, Nat Rev Cardiol. 9:360-70,2012; Scand J Work Environ Health, special issue 32. No 6 2006)

Author response

We agree that consideration of biological pathways is essential in causal inference. Potential pathways including those listed above is mentioned in the introduction and touched upon in the general discussion. This scattered information has been restructured into one more comprehensive paragraph in the discussion, which also includes the suggested reference. It now reads:

> Various pathophysiological mechanisms have been suggested to explain how psychosocial factors may influence cardiovascular disease [1] [2]. One pathway involves activation of the autonomic nervous system, leading to increased catecholamine release. This can cause acute circulatory effects such as elevated blood pressure and increased heart rate, as well as initiate an inflammatory response that may contribute to vascular damage and atherosclerosis over time. Concurrently, activation of the hypothalamus-pituitary-adrenal axis increases cortisol secretion, which, among other effects, may promote blood clot formation through effects on metabolism, platelets and coagulation factors. The former mechanism—accelerated atherosclerosis—is typically associated with long latency, while the latter—effects on coagulation—may act as a short-term trigger. However, direct evidence linking activation of the autonomic nervous system and diurnal cortisol secretion to cardiovascular disease is limited [3].
>
> Some support for a causal link between psychosocial workplace exposures and ischemic heart disease or stroke comes from evidence suggesting that factors such as job strain and effort–reward imbalance may lead to increases in established cardiovascular risk factors – such as hypertension, smoking, obesity, physical inactivity, metabolic syndrome, and various biomarkers such as blood lipids and heart rate variability [4-7]. Hereby, work stress may indirectly contribute to cardiovascular disease by influencing intermediary health behaviors.
>
> It has also been argued that workplace stressors may trigger acute cardiovascular events—such as myocardial infarction or stroke—in individuals with advanced atherosclerosis. This could occur through mechanisms including increased sympathetic activation, elevated blood pressure, a lowered arrhythmic threshold, and stimulation of inflammatory and procoagulant responses [2].
>
> In summary, workplace stressors may contribute to cardiovascular disease through both long-term effects and short-term triggering mechanisms. Although there is no shortage of plausible biological pathways, actual demonstrations that one or more of these factors mediate the relationship between workplace stressors and cardiovascular disease remain limited.

Finally, the mechanism issue is now included in the evidence synthesis:

> A large body of high-quality epidemiological studies from the past five decades addresses links between psychosocial stressors at the workplace and cardiovascular risk. The strong heterogeneity of populations and study designs precludes options for formal meta-analysis.
>
> Many studies show unresolved inconsistencies. Where risk estimates are elevated, they tend to be small or modest in magnitude. In addition, there is a likely risk of bias and confounding, with a net effect in an unpredictable direction. Furthermore, few studies demonstrate clear exposure-response relationships. Work stressors may contribute to cardiovascular disease through both short and long-term biological mechanisms but evidence that such mechanisms mediate the associations remain limited.

Reviewer

I also lack a more extensive discussion about exposure and exposure assessments. In the classification (table p 32) of evidence for causality you treat them as independent, while I think they are example of the same or similar “exposure” sometimes expressed as “strain” or “stress” or “mentally strenuous”. You also mention this in the text (e.g. p 25 para 4). In real life people are exposed to several of these exposures during their working life sometimes simultaneously. An example is a Danish bus driver who got a cardiovascular disease accepted for compensation due to “stress”[2]. Several aspects of mental “stress” are listed in that case and as it was the total “stress” that was evaluated. Therefore, I think there should be a discussion on how to interpret the classification where there are two or more factors that are at place, e.g. job strain in combination with long working hours in combination with some bullying.

Author response

We acknowledge the importance of this issue and provide the following add-on to the discussion:

> Potential additive or even interactive effects of co-exposure to several types of workplace stressors is important, in particular when exposures are not conceptually overlapping as for instance long working hours in combination with high job demands and when at least one of considered stressors is likely to have causal cardiovascular effects. Although few studies address effects of multiple exposures (e.g. [8]), there is a notable lack of such research.

Reviewer

The discussion of relevant confounders could be extended including their strength and direction. To my view confounders should be established as causal. You state that early adversity is a confounder (page 11 1st para). I am not sure that there is a causal link between such exposure and cardiovascular risk. There is also a risk of overadjustments for confounders which are partly linked to e.g. mental stress. E.g. if mental stress increase smoking or cause people starting to smoke, adjusting for smoking will severely underestimate the risks of mental stress, see e.g. figure 3 in the paper by Steptoe & Kivimäki cited above.

Author response

We have included a new paragraph in the discussion:

> We only included studies that provided risk estimates adjusted for sex, age and some measure of socio-economic position – by analysis, stratification or design. These factors are all considered strong determinants of cardiovascular disease: increased risk by male sex, higher age and lower socio-economic position. The direction of bias if these factors were not controlled may be in either direction depending on the study population and the variable distribution across groups that are compared.

Furthermore, we have updated paragraphs in the discussion addressing confounding as a likely cause of attenuated and inflated risk estimates.

Likely bias towards the null:

> Third, adjustment for behavioral risk factors (e.g., smoking, sedentary lifestyle) and medical conditions (e.g., hypertension, hypercholesterolemia) may have biased risk estimates toward the null if these factors are on the causal pathway from psychosocial stressors to cardiovascular disease. In many studies, such adjustments did indeed attenuate risk estimates. Similarly, several studies adjusted risk estimates for distress and depression which also might result in deflationary bias to the extent that these factors are mediators of observed effects.
>
> However, because these factors were typically measured only once at baseline, concurrently with exposure, they could also introduce inflationary bias if not appropriately adjusted for if they occur temporally prior to the onset of exposure.

Likely inflationary bias:

> Second, residual confounding is a concern, particularly given that any true elevation in risk is likely small or modest. Socioeconomic factors—especially education and occupational class—are strongly associated with both cardiovascular outcomes and workplace exposures such as job demands, decision authority, and skill discretion [9-14]. We only included studies that to some extent accounted for socio-economic position, but this does not imply that adjustment was sufficient. For instance, job strain remained a significant predictor when adjusted for income, but not when education was also included in the model [15].
>
> Third, several studies adjusted risk estimates for a range of other less robust antecedents of cardiovascular disease such as ethnicity, family history or personality thus limiting likely inflationary bias by these factors. However, few studies accounted for childhood adversity [16, 17], limited social network or loneliness [18, 19], and most studies did not adequately control for other workplace exposures that are closely related to the psychosocial exposures under investigation—particularly the component variables of composite measures like job strain and effort–reward imbalance.

Reviewer

I disagree with you that the use of independent exposure assessment as job-exposure-matrices should be more reliable, and the attenuated risk indicates that reports from the people are less correct (para 6 page 28). Stress or strain are typically subjective experiences by the individual. JEM is a proxy and could as such also attenuate the "true exposure".

Author response

We fully agree that stress and its biological effects are mediated by psychological processes and people's perceptions, but nevertheless we thrive to identify the occupational environment that trigger these responses. We also agree that JEMs are not inherently more 'correct' than individual reports on psychosocial exposures and likely associated with some non-differential misclassification towards the null. However, the argument is that if findings based upon self-reports are corroborated by studies applying JEMs, causal inference would become stronger. To address this point, we have substituted this sentence (in the discussion).

> Furthermore, attenuated risks in studies using independent exposure assessments (e.g. job exposure matrices) support the view that self-reports may introduce bias, even in longitudinal studies with independently ascertained outcomes.

with this sentence:

> Furthermore, studies using independent exposure assessments (e.g. job exposure matrices) did not convincingly corroborate findings obtained in the majority of studies based upon self-reported exposure assessment.

Please also acknowledge the following statement (in the summary, unchanged):

> Cause-specific mortality studies and studies using independent exposure measures, such as job exposure matrices, generally found lower risks, supporting concerns about reporting bias although it is acknowledged that such measures may less accurately capture the individual exposure and hereby result in bias towards the null.

Reviewer

Meta-analysis of observational studies is tricky and includes several possible biases. Eggers et al state that "statistical combination of data should not be a prominent component of systematic reviews of observational studies" [3]. Meta-analysis often assumes the same relative risks in all ages, which is a strong assumption especially for common diseases like cardiovascular diseases. E.g. the relative risk of myocardial infarction due to smoking seems to decrease by age[4]. Some of the studies you include have qualitative measures of exposure. The relative risk will depend on the reference population and comparing relative risks in a meta-analysis indicates that you have the same reference population or can adjust for differences in exposure in the reference population. This review seems to be requested for purposes of compensation. Then the reference population is highly important to clarify. Furthermore, your meta-analysis assumes a relative risk model over the studied ages which also is a strong assumption. If the "true" model is an additive model, such assumption may lead to biased conclusions (see e.g. Järvholm, Am J Ind Med, 21:101-6, 1992).

[3] [see e.g. Egger et al, Systematic reviews of observational studies p 211-27 in Egger M, Smith GD, Altman DG (ed) Systematic reviews in health care. Meta-analysis in context BMJ Publishing group, London 2001]

[4] Koon et al, Lancet 2006; 368: 647–58

Author response

We fully agree that premises for formal meta-analyses are violated for numerous reasons and that the pooled estimates with confidence intervals only provide a crude overview of findings across studies. Therefore, the main approach to causal inference in this report is based upon careful consideration of the classical and widely acknowledged Bradford Hill 'criteria'. In fact, we were hesitant to provide meta-analytical estimates at all but considering the large number of studies and lack of alternative ways to overview the data we decided to provide the pooled estimates while underscoring the need for critically evaluation of heterogeneity, bias, confounding as well as the Bradford Hill criteria. We explicitly address limitations of meta-analysis in the following (not changed):

> Given substantial heterogeneity across studies in terms of populations, exposure and outcome measures, and analytical strategies, pooled meta-analytic estimates should not be interpreted literally. Instead, they provide a general indication of the potential direction and magnitude of associations, within the acknowledged limitations of bias and confounding.

> The studies included in this review display substantial heterogeneity in terms of geography, population demographics, sampling procedures, exposure and outcome measures, and analytical approaches. These differences can violate assumptions of homogeneity for meta-analytic interpretation. As a result, the meta-analytic risk estimates and confidence intervals do not necessarily correspond to parameters that reflect real-world populations. These estimates should not be interpreted literally. Rather, in the absence of more suitable alternatives, they offer an approximate indication of the direction and magnitude of the effect. Their interpretation must also take into account the influence of bias and confounding

Reviewer

The reviewers´ decision to classify an exposure as "+" and e.g. not "++" is not described. Is it the size of risk estimates, the number of studies, the quality of studies (and if so which aspects), etc.?

Author response

We acknowledge that reasons for 'translating' the evidence synthesis into the simple classification requested by the Work Environment Fund were not explicit and have therefore added the following:

> The evidence synthesis was summarized according to classification requested by the Danish Work Environment Fund (for definitions see next page). A key issue is whether it 'not likely' (++) or 'not unlikely (+)' that a given exposure-outcome association can be explained by chance, bias or confounding. Because of the availability of many large high-quality epidemiological studies, chance findings were not considered an issue. The main reasons for classifying the evidence as 'limited (+)' rather than 'likely (++)' are unresolved inconsistencies across studies, risk estimates of small or modest magnitude, likely risk of bias and confounding, with a net effect in an unpredictable direction, lack of comprehensive data on exposure-response relationships and limited evidence of biological mechanisms that mediate the associations.

Reviewer

Some details:

This report will probably be read by non-scientists, and it is important that conclusions from the details are clear and reported in similar way e.g. for similar strengths of associations and confidence intervals (and other aspects if available). Typically, the language for describing risk estimates is varying – I give a few examples below. I would have preferred just tables with confidence intervals and saving the discussion of strengths of association and what that would implicate for the conclusions to the final part of the report.

"Pooled analyses showed weak associations between job strain and cardiovascular disease after full adjustment. The average variance-weighted hazard ratios (HRs) were 1.13 (95% CI 1.06–1.21, 26 studies with 49 risk estimates) for cardiovascular disease overall, 1.14 (95% CI 1.06–1.23, 21 studies with 32 risk estimates) for ischemic heart disease, and 1.19 (95% CI 1.03–1.37, 7 studies with 13 risk estimates) for stroke." (page 5)

"Iso-strain, the combination of low social support and job strain, was linked to cardiovascular disease overall the in meta-analysis with a modest strength of association (HR 1.21, 95% CI 1.06-1.38, 4 studies with 9 risk estimates)." (page 5)

"All studies consistently found that ERI was associated with ischemic heart disease overall (average meta-analytic HR 1.18, 95% CI 1.03–1.35, 3 studies with 4 risk estimates), though without clear exposure-response patterns. One study reported an association only among men. Weak associations with ischemic heart disease were noted for high effort and low reward analyzed separately (meta-analytic HR for two studies with two estimates: high effort 1.07, 95 % CI 0.85-1.36; low reward HR 1.11, 95% CI 0.92-1.34)." (page6)

"The average weighted, fully adjusted hazard ratio across the 12 cohorts was 1.05 (95% CI: 0.90–1.24). With the exception of one outlying hazard ratio of 2.47 (95% CI: 0.99–6.16), based on a small, selected Danish study population, all estimates were either below 1 (six estimates) or slightly to moderately elevated (five estimates)." (page 16) *[My comment: The broad confidence interval indicates low precision while "outlying hazard" could be interpreted that something is wrong]*

"All five studies reported higher risk es�mates than the IPD-Work Consortium study, with HR's ranging from 1.19 to 2.50. Only the smallest study reported statistically significant results (HR 2.5, 95% CI 1.1-5.6 among men) [101]. Only one study addressed the risk of stroke in relation to perceived job insecurity. This study found no increased risk (HR 0.94, 95% CI 0.63-1.40)" [99]. (page 21) [*My comment: the finding of the last study [99] is compatible with both an increased and decreased risk*]

Author response

Thanks for pointing this out. In fact, several co-authors had similar concerns and consequently we defined the use of weak/small, modest, medium and large to characterize strength of associations in the Annex on Abbreviations. Nevertheless, prompted by the reviewer remark, these terms have now been systematically erased in all cases where risk estimates with confidence intervals are mentioned – but kept in other places where appropriate and in accordance with the terminology provided in Annex I

Moreover, the specific suggestions for alternative phrases have been adopted.

Reviewer

p 32: Classification of evidence include "(+)" for low control – it is not included in the list of criteria

You use "hazard ratio", "risk" and "risk estimates" when you mostly could have used the same term. Maybe you should have a word list where you explain the terminology.

Author response

A footnote is now provided to explain the (+) in the classification of evidence table:

> 1 (+) There is limited evidence for causality. Risk estimates in most studies are close to 1 with confidence intervals including 1.

When we reference specified original studies, we use the measure of association provided by these studies (e.g. HR hazard ratio, RR relative risk, OR Odds ratio), other wise when we do not refer to a specific measure of association, we use the term ‘risk estimate’. This has now been corrected throughout.

Review by Jussi Vahtera, Professor emeritus, Department of Public Health, University of Turku, Finland, 11.9.2025.

This systematic review was commissioned by the Danish Work Environment Fund to provide an updated knowledge base to support decision-making regarding whether—and to what extent—specific workplace psychosocial exposures contribute to cardiovascular disease. Numerous recent original studies have been published which are not included in earlier systematic reviews. As trials of work stress reduction and CHD have not been done, causal inference on the effects of work stress on CHD is limited to observational data. For this reason, the aim was to focus exclusively on follow-up studies and nested case-control studies which are considered most informative for causal inference. Special attention was given to exposure-response relationships, residual confounding, bias inflating as well as attenuating risk estimates, potential modifying effects of socio-economic position and studies applying independent or objective measures of exposure.

The review was meticulously implemented. The protocol was published by the international prospective register of systematic reviews (Prospero) at the initial stage of the research before completion of the literature search. The search was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) recommendations. Two authors independently screened titles and abstracts for eligibility and resolved initial discrepancies through discussion. Applying strict predefined inclusion and exclusion criteria, 56 original studies after full-text review. An additional four eligible papers were identified through reference lists, bringing the total number of included original studies to 60. Data synthesis and statistical analysis were appropriate. The findings across the included studies were clearly presented and the strengths and weaknesses of the evidence available was critically summarized for each psychosocial exposure. However, there were a few issues I would like to address.

Reviewer

OUTCOME

The outcomes in the review were ischemic heart disease (ICD-10: I20-I25) and/or stroke (ICD-10: I61-I65) based on medical criteria only (hospital discharge diagnoses, clinical examination or death certificates). Regarding hospital discharge diagnoses and clinical examination, leaving out common CVD diagnoses, such as hypertension and hypercholesterolemia, is reasonable. But the same criteria leave out studies on workplace psychosocial exposures and total CVD mortality (ICD-10 chapter I) as an outcome, although IHD and stroke are the leading causes in the CVD deaths and many studies on work stress CVD mortality are based on all such deaths. However, there were some studies included in the review where the outcome was all CVD deaths instead of those from IHD and stroke only (eg., ref 103). Thus, there are potential inconsistencies in the included studies. In addition, it would be good to note in the general discussion that these studies were not included in the review and comment whether this might have had any effect on the findings and conclusions (eg. Kivimäki et al. Work stress and risk of cardiovascular mortality: prospective cohort study of industrial employees. BMJ 2002).

Author response

We agree that the in- and exclusion of mortality studies need clarification. To obtain a high degree of outcome specificity, we only included studies where cardiovascular mortality explicitly was due to ischemic heart disease and/or cerebrovascular disease – and not due to other underlying cardiovascular diseases such as pulmonary embolism or hypertensive disease. However, one otherwise eligible study that did not fulfill these strict criteria for outcome definition was erroneously included, namely the study mentioned by the reviewer [20]. In the revised report we have corrected this error by excluding this paper, so the total number of included papers is 59, not 60. The summary, main text, tables and annexes have been updated accordingly.

In total five mortality studies were excluded because of the strict inclusion criteria. These are briefly summarized here:

> Vahtera et al. (2004) is a highly informative population-based study that reported increased cardiovascular mortality in relation to downsizing of staff during the economic crisis in Finland in the 1990'es [21]. The exclusion of this study weakens the evidence that job-security is causally related to cardiovascular disease, but we still consider the overall evidence as limited.
>
> Kivimäki et al. (2002) is a prospective 25-year follow-up study of 812 employees in a metal industrial company [22]. Job strain and effort reward imbalance was associated with increased CVM (fully adjusted HR for job strain: 2.22 (95% CI 1.04 to 4.73) and for ERI: 2.42 (95% CI 1.02 to 5.73). Strengths include long follow-up, exposure-response data and adjustment for occupational group, medical and behavioral factors. Limitations include the crude measure of outcomes.
>
> Elovainio et al. (2006) is a prospective 27-year follow-up study of 804 employees in an engineering industrial company. High self-reported justice at work was associated with decreased CVM (fully adjusted HR 0.61 (0.36 - 1.00). Strengths include long follow-up, and adjustment for occupational group, medical and behavioral factors. Limitations include the crude measure of exposure and outcome.
>
> Toivanen et al. (2006), in a Swedish population-based study with 10.916 CVD deaths 1990-1995, found that low job control (assessed by a job exposure matrix) contributed 10% to the association between income and CVM [23].
>
> Heslop et al. (2002) is a longitudinal study of Scottish men and women and found no evidence that self-reported job dissatisfaction on one or two occasions were associated with increased risk of CVD mortality [24]. Only two other studies addressed job dissatisfaction and the exclusion of the Heslop et al paper does not justify any change of the rating of the overall evidence (inconclusive evidence).

As suggested by the reviewer we include a new paragraph in the discussion that addresses the cardiovascular mortality studies:

> We included mortality studies if the cause of death was ischemic heart disease and/or stroke. Studies including other cardiovascular outcomes such as pulmonary embolism or hypertensive disease were excluded. Since ischemic heart disease and stroke are leading causes of cardiovascular mortality, we may have missed important information. In all, five cardiovascular mortality studies were excluded by use of the strict inclusion criteria. These studies addressed job strain and effort reward imbalance [22], organisational justice [25], downsizing [21], job dissatisfaction [12] and job control [23], respectively. Although the studies are high quality epidemiological studies, they address different psychosocial exposures and are therefore not critical for the final evaluation of causal inference.

Reviewer

INTERACTIVE EFFECTS OF DEMAND AND CONTROL

One of the aims was to clarify to what extent the basic dimensions of the work stress models (eg. psychological demands and job control in the job strain model) underlie combined (interactive) effects. Only four studies were identified that had examined the effect of job strain while accounting for the separate effects of job demands and job control. The conclusion was that it remains unclear whether observed effects of job strain are primarily driven by one or more of these components, an important problem regarding implications for interpretation and practical application. However, the IPD-Work Consortium, using individual records from 13 European cohort studies (REF 84), has in the article's appendix provided data for alternative measures of job strain in four categories: low strain (low demands and high control), passive (low demands and low control), active (high demands and high control), and high strain (high demands and low control). The hazard ratios were 0·93 (95% CI 0·89–0·98) for high control and 1·02 (0·96–1·08) for high demands. With the combination of high control and low demands as comparator, the hazard ratios were 1·12 (0·99– 1·27) for low demands and low control, 1·06 (0·94–1·19) for high demands and high control, and 1·28 (1·11–1·48) for high demands and low control. Further evidence from the IPD-Work Consortium on individual and combined effects of job strain components on subsequent morbidity and mortality showed that risks are highest in individuals with job strain, whereas any effects of high occupational demands in the absence of low control, and of low job control in the absence of high demands, were weaker (REF Kivimäki et al. Individual and Combined Effects of Job Strain Components on Subsequent Morbidity and Mortality. Epidemiology 2019; 30:e29-e30). These findings support Karasek's idea that harmful psychological load often results from a combination of high demands and low job control, rather than from either of these factors alone and do not support the conclusion in this review that it remains unclear whether observed effects of job strain are primarily driven by one or more of these components.

Author response

We acknowledge that the issue of interactive effects of the main dimensions of the demand-control-support work stress model and the effort-reward imbalance model may need a more elaborate discussion to reflect opinions shared by several leading scientists in the field.

The current paragraph in the discussion of the JC model reads:

> Only four studies examined the effect of job strain while accounting for the separate effects of job demands, job control, and social support. It therefore remains unclear whether observed effects of job strain are primarily driven by one or more of these components. This has important implications for interpretation and practical application.

This paragraph has been rewritten as follows:

> Only four studies examined the effect of job strain while accounting for the separate effects of job demands, job control, and social support [26-29]. None of these found significant associations between job strain (the product term in the model) and cardiovascular disease. However, other researchers have addressed the issue of combined effects of high job demands and low job control by stratified analysis of combinations of median split dichotomies of job demands and job control (often referred to as 'the quadrant method'). Thus, the IPD-Work Consortium compiled data on risk of myocardial infarction in 13 European cohorts according to these categories. [30]. Using the group with high control and low demands as the reference group, the hazard ratio was 1.12 (95% CI 0.99– 1.27) for low demands and low control, 1.06 (95% CI 0.94–1.19) for high demands and high control, and 1.28 (95% CI 1.11–1.48) for high demands

and low control (job strain) [31], indicating that the combination of high demands and low control (job strain) produces the most robust effect compared with each of these factors alone. These risk estimates were only adjusted for sex and age. In a revised analysis from 2019, risk estimates were also adjusted for socioeconomic class [32]. The revised median split quadrant hazard ratios were 1.07 (95% CI 0.90-1.27) for the combination of low demands and low control, 1.09 (95% CI 0.97-1.23) for high demands and high control and 1.21 (95% CI 1.05-1.39) for high demands and low control (job strain). From the revised numbers the expected hazard ratio of the combined independent effect of demands and control would be approximately 1.09 x1.07=1.17, close the estimated hazard ratio of job strain assuming multiplicative interaction. Furthermore, when also considering the findings from the four studies that included formal statistical tests for interaction using multiplicative models [26-29], it remains unclear whether the observed effects of job strain are primarily driven by one or more of its specific components. This uncertainty has important implications for both interpretation and practical application.

Reviewer

CAUSAL INFERENCE

An important aim was to assess whether the associations between psychosocial exposures and cardiovascular outcomes were informative for causal inference. The overall conclusion was that the evidence supporting a causal link between the exposure and the risk of CVD is limited. This conclusion resulted from the unresolved inconsistencies across many studies, the small magnitude of risk estimates when elevated, the likely presence of bias and confounding with unpredictable net effects, and the absence of demonstrated exposure–response relationships. I fully agree with the conclusion. However, study designs that support causal inference in observational data were not explicitly identified nor discussed. A key limitation in an observational design is that the exposure and the risk factors are correlated resulting in unbalanced comparison between the exposed and the unexposed in relation to the risk factors. Closest to randomized trials are natural experiments where the characteristics of the participants are measured before the exposure, and the exposure is random in relation to these characteristics. The studies examining the effects of downsizing on CVD are examples of a natural experiment. Another way of emulating a target trial are within-individual studies (eg. case crossover studies) which effectively control for all time-invariant confounders. A third example are pseudo-trials building on repeated information on the exposure and applying strict predefined inclusion and exclusion criteria to ensure temporality between the exposure and the outcomes. Unfortunately, as the review shows, such study designs are rarely utilized. It might be worth highlighting in the general discussion the potential of such study designs when examining the effects of psychosocial exposures on CVD.

Author response

We agree. Unfortunately, there are few studies on workplace stressors and cardiovascular disease that apply study designs that come close to classic randomized controlled study. In a new brief paragraph, we touch upon this issue:

> Moreover, few observational studies on workplace stressors and cardiovascular disease apply study designs that emulate the classic randomized controlled study. Studies on health effects of major downsizing of company staffs during period with economic crises may be considered a natural experiment of effects of downsizing [21, 33]. A range of other design options are available but often not easily applied in psychosocial epidemiology [34].

Reviewer

A minor point. P. 25, last sentence: "However, in that study there were no indications of exposure-response relationships and no fully adjusted analyses [117]". In fact, this Whitehall II Study shows that the associations between job strain, ERI and justice followed a gradient; that these associations were not accounted for by baseline risk factors; and that the association between the level of justice and CHD was also independent of job strain and effort-reward imbalance. Note that these exposure-response relationships were also shown for job strain and ERI.

Author response

The Whitehall II study addressing organisational justice [35] reports that the association between incident coronary heart disease and intermediate level of justice at work was HR 1.12 (95% CI 0.83-1.51) and for high level of justice at work HR was 0.71 (95% CI 0.51-0.99), Table 2. Therefore: no indication of exposure-response. These analyses were adjusted for behavioral and medical risk factors, age and employment grade but not for family status and ethnicity and were therefore not fully adjusted. Results for job strain and ERI are considered and reviewed based upon data in other papers that explicitly address these exposures. Consequently, we do not see any need for update of the original text.

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