HORIZON 2020

PROJECT DELIVERABLE REPORT

OActive

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Advanced personalised, multi-scale computer models preventing osteoarthritis

SC1-PM-17-2017 - Personalised computer models and in-silico systems for well-being

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Revision History

Version	Date	Responsible	Description/Remarks/Reason for changes
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Abbreviations

OA	osteoarthritis
ICF	International Classification of Functioning, Health and Disability
CINAHL	Cumulative Index to Nursing and Allied Health Literature
PROSPERO	Prospective Register of Systematic Reviews

1   Summary of the deliverable

This deliverable includes the "Documentation of social attributes and interdependencies of cognitive and social determinants". More precise, this deliverable will contain a detailed documentation of the social attributes and the description of the complex interdependencies and interactions between the different social factor families (social position, social context, psychological influences, personal factors) (p.26 project plan).

2   Introduction

Given the increasing prevalence of knee osteoarthritis world-wide[1,2], the research community is challenged to urgently **identify factors that predict its onset and progression** with the ultimate aim to mechanistically understand disease and develop interventions that reduce burden to patients and society. This task is complicated by the apparently heterogeneous pathways that lead to the typical clinical and imaging presentation of knee osteoarthritis, namely loading-related knee pain, crepitus during active joint movements, modest joint effusion, as well as cartilage degeneration, osteophytes and subchondral bone marrow adaptations on plain radiographs or magnetic resonance imaging[3]. Indeed, knee osteoarthritis can be part of a seemingly idiopathic localised or generalised joint problem, or seen secondary to other events such as trauma of end-stage destructive inflammatory joint disorders[4]. No doubt this affects what factors relate to knee osteoarthritis and/or their predictive power. Interestingly also, several reports confirmed that signs and symptoms of patients show variable and rather small associations with local joint disease features[5], suggesting that predictors of structural (e.g. joint space narrowing) and functional aspects of disease (e.g. pain) may be congruent or differ profoundly.

Traditionally, risk factors for knee osteoarthritis are considered local to the joint or systemic referring to whole-body systems. Excellent reviews on these classical risk factors of knee osteoarthritis incidence and progression exist and consistently identified older age, female gender, obesity, excess occupational loading, low vitamin D and non-Caucasian race/ethnicity as unfavourable systemic characteristics[6,7]. Local risk factors clearly included knee injury, especially anterior cruciate tears, whereas the role of muscle strength, knee alignment or leg length inequality remains controversial. **Unfortunately, the majority of studies did not fully consider a biopsychosocial view on risk factors and ignored the contextual influences such as social**

position on knee osteoarthritis profiles[8]. Nevertheless, there are clear indications in the scientific literature that contextual factors merit consideration and scientific scrutiny. For example, Jorgensen et al.[9] assessed the level of education and found that even a basic education level may be associated with reduced risk of developing knee OA, whereas other studies were conflicting.

The traditional model on risk factors for knee OA that merely focuses on impaired local or whole-body patho-anatomical features (body functions and structures) in knee OA needs adaptation. **Several steps are needed to move forward.** Firstly, candidate risk factors for knee OA should be clearly defined within a broadly-scoped, biopsychosocially-oriented 'taxonomy' or 'classification' of health-related concepts. Secondly, a model on how to operationalise the study risk factors in knee OA should be proposed. Key outcomes to predict in this model should be defined. Also, the nature of each risk factor should be hypothesised, whereby typically prognostic, mediated, moderated and predictor effects are considered. Lastly, the model should be validated and reveal mechanistic relations between its components.

Well-aware of the challenges described above, the OActive project a-priori proposed an increased focus on concurrently studying the impact of contextual factors (such as socioeconomic attributes) and disease-related outcomes on target knee OA outcomes. Deliverable 5.3 reports on the steps taken within the OActive project's Task 5.3 to deepen our understanding of risk factors in knee OA, as well as a discussion of future research venues. Also, the link with other work packages will be discussed where appropriate.

Firstly, a detailed taxonomy of contextual factors with guiding definitions, together termed the **'OActive contextual factors framework'**, was built. Relevant prospective cohorts on knee osteoarthritis with their measurement instruments (e.g. OsteoArthritis Initiative, European Project on OsteoArthritis, EVolution of knee Osteoarthritis LeuVEn) were mapped onto this novel framework to develop a questionnaire for use in the OActive Data Collection Protocol.

Secondly, candidate contextual factors that have been grouped thematically (e.g. housing, employments, etc.) were translated in bibliographic search strings to study their use in the scientific literature i.e. a **preparatory scoping systematic literature review**.

Thirdly and depending on the number of research papers retrieved for each thematic group (major review to include 7K-10K articles), the **use of contextual factors**, especially socioeconomic factors, was assessed in knee OA **via a full scoping systematic literature review**. State-of-the-
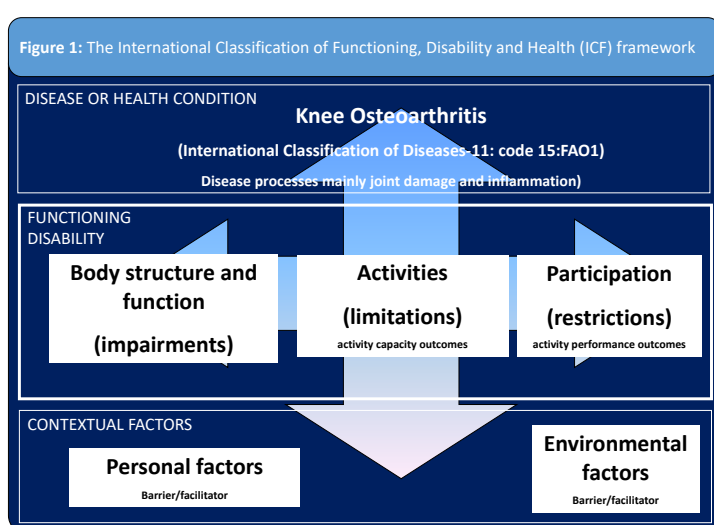
art methodology based on the Cochrane guidelines was implemented for this task. Outcomes of interest were the broad spectrum of functioning (body structures, body functions, activities and participation): pain, function, physical activity, structural OA status and progression, clinical examination outcomes and health-related quality of life.

Lastly to link Task 5.3 to the OActive hypermodel under development in work package 6, a **protocol extension** to the scoping systematic literature review was developed **to quantify the effect of socioeconomic factors** on knee OA outcomes and compare the results with the OActive hypermodel (the results are beyond the scope of D5.3).

3   OActive framework on contextual factors

3.1   Development of the taxonomy

We aligned our framework of contextual risk factors in knee OA with the contemporary definition of health to ensure a broad scope of health-related concepts: "a state of physical, mental and social well-being in which disease and infirmity are absent"[10]. Especially helpful was the World Health Organization' family of classifications: the International Classification of Diseases (ICD-11), the International Classification of Functioning, Disability and Health (ICF) and the International Classifications of Health Interventions (ICDHI-1, draft version). ICD-11 focuses on the etiology of disease by providing a detailed list of medical diagnoses (knee OA is classified under "Chapter 15: Diseases of the musculoskeletal system or connective tissue/FA01 Osteoarthritis of knee), while the more recent ICDHI-1 is an attempt to classify health interventions by their Target, Action and Means. Most relevant in the context of risk factors was the International Classification of Functioning, Disability and Health (ICF) multidimensional framework to describe health and health-related components of well-being (Figure 1).

Figure 1: The International Classification of Functioning, Disability and Health (ICF) framework

DISEASE OR HEALTH CONDITION
Knee Osteoarthritis
(International Classification of Diseases-11: code 15:FAO1)
Disease processes mainly joint damage and inflammation)

FUNCTIONING DISABILITY
Body structure and function (impairments)
Activities (limitations) activity capacity outcomes
Participation (restrictions) activity performance outcomes

CONTEXTUAL FACTORS
Personal factors Barrier/facilitator
Environmental factors Barrier/facilitator

Within ICF, the core concept functioning serves as the umbrella terms to capture the perspective of the human organism and its entities (body structures and function component), of the whole person and his/her actions (activities component) and of the whole person and his/her actions in a societal context (participation component). Similar but negatively phrased, disability serves as the umbrella term for impairments in body structures and functions, limitations in activities and restrictions in participation. Health conditions and *contextual factors*, namely personal factors and environmental factors, interact with functioning and disability and underscore the biopsychosocial nature of the ICF. For completeness, one should mention that each ICF component is further hierarchically subdivided into chapters/domains and categories at varying levels of granularity (up to 4) with a numerical code for each level (total approximately 1454). Table 1 presented a summary of ICF concepts. World Health Organization (WHO) encourages the development of brief and extensive ICF core sets of domains and categories per health condition, typically containing around 30 and 90 items respectively. Endorsed Core Sets exist for osteoarthritis in general, but not for knee OA.

Together, the WHO classifications provided a solid base for a taxonomy on risk factors of knee OA Importantly, these classifications offer a comprehensive descriptive framework, but do not offer mechanism-based relationships between its components that for example may guide clinical reasoning or model validation. Also, personal factors are currently not classified, rendering the taxonomy incomplete.[11] Therefore, we searched the literature for attempts to elaborate personal factors and incorporated these finding in our new taxonomy. To additionally capture key opinions of different stakeholders, the following inputs mainly from the literature were combined: the perspective of patients with knee OA, expert researchers (S.V. & T.S.) and care providers, as well as prospective cohorts in knee OA (Osteoarthritis Initiative, European Project on OsteoArthritis, EVolution of knee Osteoarthritis LeuVEn).

The full taxonomy (current version 2.0) consists of over 350 contextual factors, about 100 personal factors and about 150 environmental factors. For each factor, the presence in major OA cohorts is given. The EVOLVE cohort covered the taxonomy best, while OAI contains few contextual factors. A snapshot of the OActive contextual factors framework can be found in Appendix 1. The full version is available on simple request to the project lead or via this link:

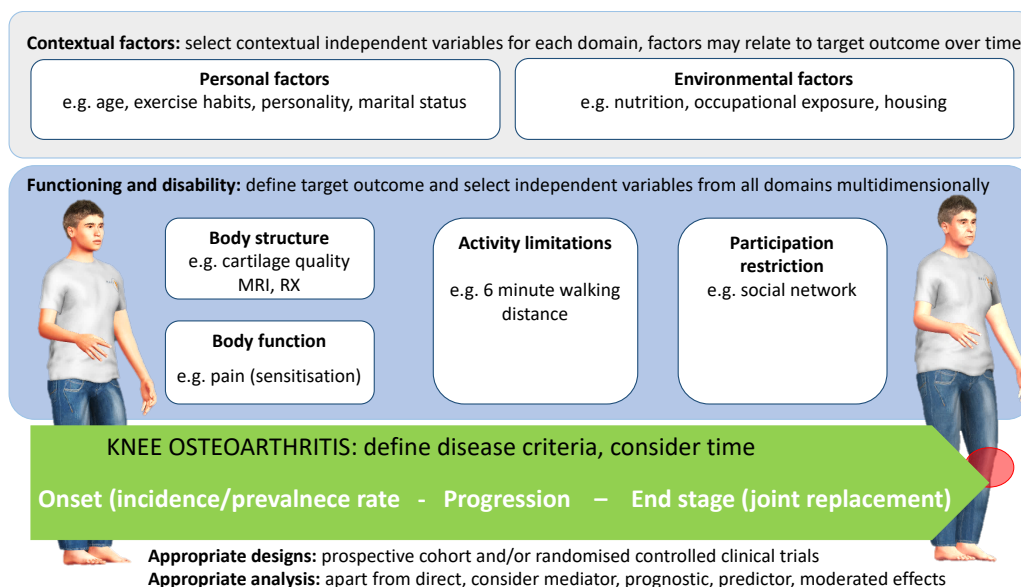https://kuleuven.box.com/s/4zkd9f6dkfvzpneeoouorg1fyvhx8dyr .

3.2   Pilot implementations of the novel framework

Firstly, in support of the clinical centers within the OActive consortium, guidance on contextual factors to include in the **self-reported clinical questionnaire was provided** based on the novel framework (see Data Collection Protocol, available on the Freedcamp respository of OActive or simple request to the project lead). This clinical questionnaire includes a highly feasible set of contextual factors, namely age, sex, marital status, country of birth, level of education, residency, housing ownership, household income and occupation.

Secondly, the novel framework was **translated into a model to concurrently study the impact of contextual factors and disease-related outcomes** on target outcomes in knee OA (see Figure 2). Key guiding aspects in this model are the need 1) to select at least one outcome in each health domain to ensure multidimensionality, 2) to separate structural and functional outcomes regardless whether they are dependent or independent variables in the predictive model of choice and 3) to check if variables act as mediator, moderator, prognostic or predictive factor.

Figure 2. Proposed model to concurrently study the impact of contextual factors and disease-related outcomes on target knee OA.

4 Summarizing the literature on contextual factors in knee osteoarthritis

4.1 Preparatory scoping review on the use of contextual factors in knee osteoarthritis

In line with the OActive contextual factors framework, all contextual factors were subsequently converted into bibliographic search terms. Thematic groups of search terms (e.g. nutrition, occupational exposure, built environment) were created and translated in bibliographic search strings to study their use in the scientific literature i.e. a short scoping literature review in preparation of a feasible full scoping review analysis. Entry of candidate factors during the scoping review phase was limited to the Medline (PubMed) database. Socioeconomic factors resulted in a coherent set of articles, whereas factors related to food, built environment (such as mountains, not related to social position), fauna and flora, occupational loading increased the number of irrelevant retrieved articles dramatically. For example: studies related to food mainly assessed the effects of specific supplements (e.g. glucosamine sulphate) or exposure to specific diets and were thus irrelevant to social influences. Similarly, excellent systematic reviews summarizing the link between occupational exposure and OA onset were already available, but focussed on biomechanics involved rather that social factors. As these topics only indirectly reflect social position at best, they were considered beyond the scope of this work package focusing on social position/context and were therefore excluded. For the same reason as well as to keep the review feasible (<10 000 research articles to screen for a major literature review), the factors built environment, fauna and flora were excluded. The final list of factor clusters (>200 search terms) included synonyms of social position and related factors income, health disparity, inequity, inequality, housing, family characteristics, employment, insurance, education, ethnicity and race, together termed socioeconomic factors (Appendix 3).

4.2 Full scoping review on the use of contextual factors in knee osteoarthritis

In this section the methodology and main results for the full scoping review were described.

4.2.1 Research questions

The following research questions were addressed: 1) How often were socioeconomic factors reported in the scientific literature when studying pain, function, physical activity, structural OA status and progression, clinical examination outcomes and quality of life in knee osteoarthritis; 2) Which measurement instruments are implemented to assess socioeconomic factors in knee osteoarthritis?

4.2.2   Design

Systematic scoping literature review.

This report was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12]

4.2.3   Procedures

The following electronic bibliographic databases were screened for relevant research articles: Medline (PubMed), Embase, CINAHL, Web of Science (psych articles) and Cochrane. The final search string (Appendix 3) developed in the preparatory scoping review was executed in each database and results were merged within the Endnote software package. The first concept included terms to identify the knee osteoarthritis population. The second concept consisted of over 200 terms to highlight socioeconomic factors. No search terms were included for relevant outcomes. This ensured an appropriate sensitivity, since any search for outcomes has an inherent risk of missing studies. The removal of duplicates was performed according to the Bramer de-duplication methodology.[13] References were imported in the Rayyan software package for screening by title, abstract and keywords. Two blinded readers (TWS, MW) were appointed for screening each article, with another reader (SV) available to resolve conflicts.

We a-priori defined a flow for the screening process, where consecutively the population, presence of socioeconomic factors and their handling in the data analysis, the target outcomes (see above), study design, language, and publication type were appraised. Reasons for exclusion were recorded, and for each included article the following target outcomes were defined: pain, function, physical activity, structural OA status and progression, clinical examination outcomes and quality of life.

4.2.4   In- and exclusion criteria for retrieved studies

The PICOSS method was applied to decide whether studies were included in the scoping review:

-**Population:**   Patients with uni- or bilateral knee osteoarthritis without knee arthroplasty. Case definition could include both classification criteria or self-reported knee osteoarthritis.

-**Interventions:**   No restrictions.

-**Comparisons:**   Quantification of the relationship between socioeconomic factors on health outcomes in knee osteoarthritis.

-**Outcomes:**   Target health outcomes include pain, function, physical activity, structural OA status and progression, clinical examination outcomes or quality of life.

-**Settings:**   No restrictions.

-**Study design:**   Randomised controlled clinical trials, observational cohort studies and case-control studies, in persons aged above 16 years, without any year limit, written in English or Dutch

Exclusion criteria were: 1) study not digitally available through the library network and after request via the corresponding author, 2) not meeting the PICOSS above.
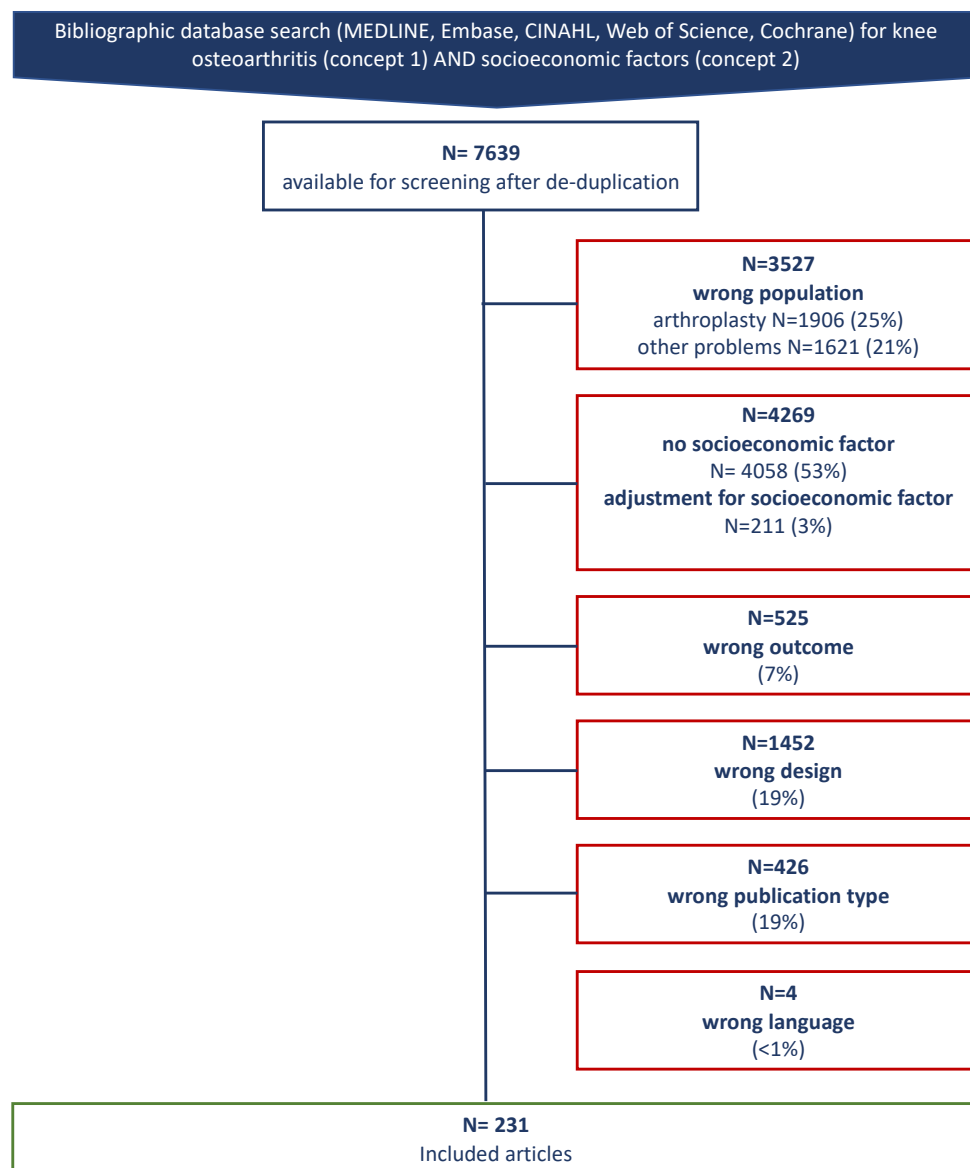
4.2.5 Data analysis

Information on the presence or absence of socioeconomic factors, their measurement tools and the target clinical knee OA outcomes of interest were manually coded in a data extraction sheet using the Rayyan and Excel software packages. Given the explorative nature of this scoping review, descriptive statistics (frequencies, percentages) were calculated as appropriate.
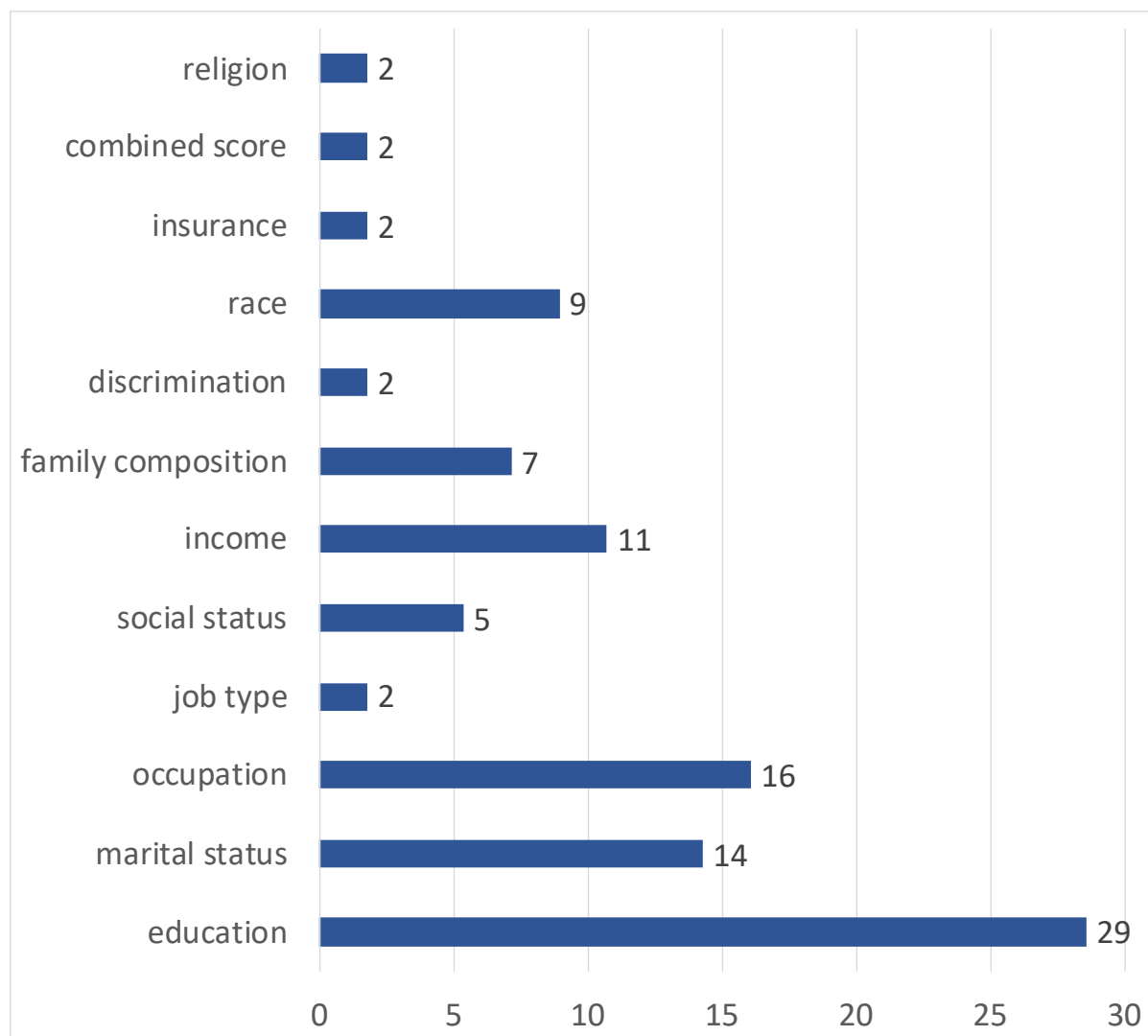
4.2.6 Results

After de-duplication, 7639 articles were available for screening (see flow chart Figure 3). Readers resolved 120 conflicts (1.6% of all studies) without the need for a third reader. The knee osteoarthritis population was confirmed in 4112 articles (1906, 25% excluded because of knee arthroplasty and 1621, 21% because of other issues related the population definition). Some interesting studies were lost because hip and knee OA was combined. Also, socioeconomic factors were more often studied in knee arthroplasty, especially in relation to access to care. Socioeconomic factors were lacking in 4058 (53%) papers and adjusted for in 211 (3%) articles. Extrapolation this finding to the body of literature on knee OA (N=39720 * 0.25 * 0.56), socioeconomic factors seem to be underreported (14%). A total of 231 (3%) papers was finally included for further scoping review.

Pain (n=110, 48%), function (n=81, 36%), physical (in)activity (n=5%), structural OA status and progression (n=7, 3%), OA prevalence or risk (n=98, 43%), clinical examination outcomes (n=10, 12%) and quality of life (n=18, 8%) were the outcomes of interest in the included studies. It was decided to first focus on pain and function for further analysis on types of socioeconomic factors, given their clinical relevance.

Figure 3: Flow chart of the screening process in the scoping review on contextual factors.

A total of 12 different socioeconomic factors were found in the literature (Figure 4). Education was by far the most reported socioeconomic factor in the literature (n=29, 51%), next to occupational status (n=16, 28%), marital status (n=14, 26%), income (n=11, 19%), race/ethnicity (n=9, 16%), family composition (n=7, 13%), social status (n=5, 10%), discrimination (n=2, 3%), insurance (n=2, 3%), combined scores (n=2, 3%), job type (n=2, 3%), religion (n=2, 3%). Although several studies assessed the same factor, the measurement instruments used differed dramatically, mainly in ordinal categories. The full data extraction per study is available on simple request from the project lead. Socioeconomic factors were analysed in a subset of included papers (n=56).

Figure 4. Overview of socioeconomic factors found in the knee osteoarthritis literature by number.

4.3 Protocol extension for a systematic review on the effect of socioeconomic factors on pain and function in knee OA

The protocol described under 4.2 was extended to allow for the analysis of the effect of socioeconomic factors on knee OA outcomes pain and function. The following additions applied:

1) The combined protocol will be registered at the PROSPERO database when the data extraction starts to ensure scientific integrity.
2) A more extensive data extraction sheet was developed to extract content of papers including pain and/or function. It was based on clinical expertise of our team and available quality in reporting guidelines (STrengthening the Reporting of OBservational studies in

Epidemiology, STROBE[14]; Consolidated Standards of Reporting Trials, CONSORT[15]), as well quality appraisal tools in the literature, see below. Also, information on how socioeconomic factors were used in the statistical analysis were captured. We considered mediation, moderation, prognostic and predicted effects.[16,17]

3) Formal quality assessment was organized using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2), Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) and the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies.[18,19]

4) Results will be statistically pooled when appropriate. Also, outcomes will be compared to the output of the OActive hypermodel under development in work package 6. Recommendations on what socioeconomic factors seem most powerful and how to assess them in knee OA will be formulated for future research. Although not part of D5.3, the results will be added to this deliverable report.

5   Conclusions

The envisioned major outputs related to D5.3 were a novel taxonomy and measurement model of contextual factors in knee osteoarthritis, in combination with a scoping overview of the contemporary literature on these contextual factors. Currently few studies focus on contextual socioeconomic factors and their assessment is methodologically highly variable. Based on this work, we can recommend a feasible set of contextual factors to include in knee OA trials and propose common measurement instruments. As a next step, international consensus can be sought on the use of contextual factors in research studies via major societies working in the field of knee OA.

6   Appendices

Appendix 1: Key definitions on the ICF classification

Table 1: Terminology used within the ICF framework	
ICF concepts	Operational definitions
Body structures and function component	
Body Functions	Physiological functions of body systems (including psychological functions). Prefix b.
Body Structures	Anatomical parts of the body such as organs, limbs and their components. Prefix s.
*Impairments	Impairments are problems in body function or structure such as a significant deviation or loss. Integrity is the positively phrased concept.
**Impairment qualifier	Indication of the extent or magnitude of an impairment
Activities component	
Activity	The execution of a task or action by an individual. Prefix a or d.
*Activity limitations	Difficulties an individual may have in executing activities.
**Capacity qualifier	The ability to execute a task or action by an individual in a standardized environment.
Participation component	
Participation	Is involvement in a life situation. Prefix p or d.
*Participation restrictions	Problems an individual may experience in involvement in life situations.
**Performance qualifier	The ability to execute a task or action by an individual in his/her current environment, including his/her societal context.
Context component	
Personal factors	The particular background of an individual's life and living, comprising the features of an individual that are not part of a health condition or a health state. (currently not classified)
Environmental factors	Environmental Factors make up the physical, social and attitudinal environment in which people live and conduct their lives. Prefix e.

*Environmental barrier or facilitator	External factor to the individual that can have a positive or negative influence on the individual's functioning and disability
**Qualifier in environment	Negative and positive scale to denote the extent of barriers and facilitators respectively
Coding processes	
First to fourth level coding	The hierarchical structure of ICF consists of a first (e.g. b**2**), a second (eg. b2**10**), a third (e.g. b210**0**) or a fourth (e.g. b2100**0**) level, depending on the granularity within the component. The first level are called chapters or domains. Further subdivisions are denoted categories.
Qualifiers	Qualifiers allow for the assessment of each ICF functioning domain or category by assigning a number from 0 (no problem, 0-4% of the time present) tot 4 (complete problem, 96-100% of the time present), or 8 (not specified) and 9 (not applicable). Similarly, environmental factors are scored as facilitators or barriers on a positive or negative 0 (no) to 4 (complete) scale, respectively.

Legenda: Positively phrased ICF components in blue, negatively phrased identical components in white with *; Qualifiers for the assessment of components in light grey with **.

Appendix 2: Snapshot of the OActive contextual factors framework

code	construct	operational definition	EPOSA included?	LC included?	OAI included?
Oactive Contextual Factors Framework					
PERSONAL FACTORS					
	General personal characteristics (Chapter 1)	This chapter addresses the inherent general characteristics such as age, sex and genetic factors that may have an effect on a person's health. This chapter does not cover characteristics that correlate to impaired health status or a disease.			
i110	Age	Age including chronological, psychological and biological age			
i1100	Chronological age	A person's age as calculated from their date of birth to the present day	1	1	1
i1101	Psychosocial age	A person's age as defined by their emotional and social development			
i1102	Biological age	A person's age in terms of biological aging factors; this can deviate from their chronological age (e.g. premature or delayed aging)			
i1108	Age, other specified				
i1109	Age, unspecified				
i120	Sex	The status of belonging to a sex (male/female/intersexual) as defined by biological terms and the gender role (how the sexual self is experienced and lived)			
i1200	Biological sex		1	1	1
i1201	Gender role				
i1208	Sex, other specified				
i1209	Sex, unspecified				
i130	Genetic factors	A person's hereditary characteristics that can influence diseases and have other effects on health (excl.: biological sex)			
i1300	Genetic factors				1
i1308	Genetic factors, other specified				
i1309	Genetic factors, unspecified				

Appendix 3: Overview of the bibliographic search string

Concept 1: Knee OA population without arthroplasty

PubMed

"Osteoarthritis, Knee"[Mesh] OR (("osteoarthritis"[MeSH Terms] OR "osteoarthritis"[Tiab] OR "osteo-arthritis"[Tiab] OR "Osteoarthrosis"[Tiab] OR "Osteo-arthrosis"[Tiab] OR "Osteoarthroses"[Tiab] OR "Arthritis, Degenerative"[Tiab] OR "Arthritides, Degenerative"[Tiab] OR "Degenerative Arthritides"[Tiab] OR "Degenerative Arthritis"[Tiab] OR "Arthrosis"[Tiab] OR "Arthroses"[Tiab] OR "Osteoarthritides"[Tiab]) AND ("knee"[MeSH Terms] OR "knee*"[Tiab] OR "knee joint"[MeSH Terms]))

Embase

'knee osteoarthritis'/exp OR (('osteoarthritis'/exp OR 'osteoarthritis':ti,ab,kw OR 'osteo-arthritis':ti,ab,kw OR 'osteoarthrosis':ti,ab,kw OR 'osteo-arthrosis':ti,ab,kw OR 'osteoarthroses':ti,ab,kw OR 'Arthritis, Degenerative':ti,ab,kw OR 'Arthritides, Degenerative':ti,ab,kw OR "Degenerative Arthritides":ti,ab,kw OR "Degenerative Arthritis":ti,ab,kw OR "Arthrosis":ti,ab,kw OR "Arthroses":ti,ab,kw OR 'osteoarthritides':ti,ab,kw) AND ('knee'/exp OR 'knee*':ti,ab,kw))

NOT 'conference abstract':it

([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim) AND [embase]/lim

Web of Science

TI=("knee osteoarthritis" OR (("osteoarthritis" OR "osteoarthritis" OR "osteo-arthritis" OR "osteoarthrosis" OR "osteo-arthrosis" OR "osteoarthroses" OR "Arthritis, Degenerative" OR "Arthritides, Degenerative" OR "Degenerative Arthritides" OR "Degenerative Arthritis" OR "Arthrosis" OR "Arthroses" OR "osteoarthritides") AND ("knee" OR "knee*"))) OR

AB=("knee osteoarthritis" OR (("osteoarthritis" OR "osteoarthritis" OR "osteo-arthritis" OR "osteoarthrosis" OR "osteo-arthrosis" OR "osteoarthroses" OR "Arthritis, Degenerative" OR "Arthritides, Degenerative" OR "Degenerative Arthritides" OR "Degenerative Arthritis" OR "Arthrosis" OR "Arthroses" OR "osteoarthritides") AND ("knee" OR "knee*"))) OR

AK=("knee osteoarthritis" OR (("osteoarthritis" OR "osteoarthritis" OR "osteo-arthritis" OR "osteoarthrosis" OR "osteo-arthrosis" OR "osteoarthroses" OR "Arthritis, Degenerative" OR "Arthritides, Degenerative" OR "Degenerative Arthritides" OR "Degenerative Arthritis" OR "Arthrosis" OR "Arthroses" OR "osteoarthritides") AND ("knee" OR "knee*")))

Cinahl

(MH "Osteoarthritis, Knee" OR ((MH "osteoarthritis" AND (MH "knee" OR MH "knee joint")))) OR

AB ("knee osteoarthritis" OR (("osteoarthritis" OR "osteoarthritis" OR "osteo-arthritis" OR "osteoarthrosis" OR "osteo-arthrosis" OR "osteoarthroses" OR "Arthritis, Degenerative" OR "Arthritides, Degenerative" OR "Degenerative Arthritides" OR "Degenerative Arthritis" OR "Arthrosis" OR "Arthroses" OR "osteoarthritides") AND ("knee" OR "knee*"))) OR

TI ("knee osteoarthritis" OR (("osteoarthritis" OR "osteoarthritis" OR "osteo-arthritis" OR "osteoarthrosis" OR "osteo-arthrosis" OR "osteoarthroses" OR "Arthritis, Degenerative" OR "Arthritides, Degenerative" OR "Degenerative Arthritides" OR "Degenerative Arthritis" OR "Arthrosis" OR "Arthroses" OR "osteoarthritides") AND ("knee" OR "knee*")))

Cochrane

[mh "Osteoarthritis, Knee"] OR (([mh "osteoarthritis"] OR "osteoarthritis":ti,ab,kw OR "osteo-arthritis":ti,ab,kw OR "Osteoarthrosis":ti,ab,kw OR "Osteo-arthrosis":ti,ab,kw OR "Osteoarthroses":ti,ab,kw OR "Arthritis, Degenerative":ti,ab,kw OR "Arthritides, Degenerative":ti,ab,kw OR "Degenerative Arthritides":ti,ab,kw OR "Degenerative Arthritis":ti,ab,kw OR "Arthrosis":ti,ab,kw OR "Arthroses":ti,ab,kw OR "Osteoarthritides":ti,ab,kw) AND ([mh "knee"] OR "knee*":ti,ab,kw OR [mh "knee joint"]))

Concept 2: Socioeconomic factors

Pubmed

"socioeconomic factors"[Mesh Terms] OR "socioeconomic factor"[Tiab] OR "socioeconomic factors"[Tiab] OR inequalit*[Tiab] OR "standard of living"[Tiab] OR "living standard"[Tiab] OR "living standards"[Tiab] OR "high-income"[Tiab] OR "middle-income"[Tiab] OR "low-income"[Tiab] OR "social class"[Mesh Terms] OR "social class"[Tiab] OR "social classes"[Tiab] OR caste[Tiab] OR castes[Tiab] OR "pay equity"[Tiab] OR "pay equities"[Tiab] OR "job ladder"[Tiab] OR "job ladders"[Tiab] OR "career ladder"[Tiab] OR "career ladders"[Tiab] OR "social development"[Tiab] OR "social developments"[Tiab] OR "social evolution"[Tiab] OR socioeconomic*[Tiab] OR "socioeconomic status"[Tiab] OR "social status" [Tiab] OR "socioeconomic position"[Tiab] OR "social hierarchy"[Tiab] OR "social structure"[Tiab] OR "social structures"[Tiab] OR sociocultural*[Tiab] OR "social factor" [Tiab] OR "social factors"[Tiab] OR "social marginalization"[Mesh Terms] OR "social marginalization"[Tiab] OR "working poor"[Mesh Terms] OR "working poor"[Tiab] OR "urban population"[Mesh Terms] OR "urban population"[Tiab] OR "urban populations"[Tiab] OR "vulnerable populations"[Mesh Terms] OR "vulnerable population"[Tiab] OR "vulnerable populations"[Tiab] OR "social determinants of health"[Mesh Terms] OR "social

determinants of health"[Tiab] OR "health status disparities"[Mesh Terms] OR "health status disparity"[Tiab] OR "health status disparities"[Tiab] OR "health disparity"[Tiab] OR "health disparities"[Tiab] OR disparity[Tiab] OR disparities[Tiab] OR inequity[Tiab] OR inequities[Tiab] OR inequality[Tiab] OR inequalities[Tiab] OR "social segregation"[Mesh Terms] OR "social segregation"[Tiab] OR "social segregations" [Tiab] OR "life situation"[Tiab] OR "living arrangement"[Tiab] OR "living arrangements"[Tiab] OR "family size"[Tiab] OR "family sizes"[Tiab] OR "family characteristics"[Mesh Terms] OR generation*[Tiab] OR "social problem"[Tiab] OR "social problems"[Tiab] OR deprivation[Tiab] OR "social isolation"[Tiab] OR "social isolations"[Tiab] OR starvation[Tiab] OR starvations[Tiab] OR famine*[Tiab] OR "unemployment benefit"[Tiab] OR "unemployment benefits"[Tiab] OR finance*[Tiab] OR "financial problem"[Tiab] OR "financial problems"[Tiab] OR

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Embase

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Web of science

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"work" OR "work" OR "occupation" OR "occupation*" OR "profession" OR "professions" OR "job" OR "jobs" OR "vocation*" OR "employment status" OR "employment*" OR "unemployment*" OR "underemployment*" OR "retirement benefit*" OR "pension" OR "pension" OR "insurance" OR "insurance" OR "unemployment" OR "liquidit*" OR "creditworthiness" OR "wealth" OR "wealth" OR "medically uninsured" OR "uninsured" OR "occupationial health" OR "occupational health" OR "workplace*" OR

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OR "demography" OR "developing countr*" OR "ethnic group" OR "ethnic group*" OR "minority group" OR "minority group*" OR "ethnic*" "minority population*" OR "nationality" OR "nationalit*" OR "population group" OR "Race Factor*" OR "race" OR "race*" OR "racial*" OR "race relation" OR "race relation*" OR "interracial relation*" OR "ancestry group" OR "ancestry group*" OR "continental population group*"

CINAHL

(MH "socioeconomic factors+" OR MH "social class+" OR MH "social marginalization+" OR MH "working poor+" OR MH "urban population+" OR MH "vulnerable populations+" OR MH "social determinants of health+" OR MH "health status disparities+" OR MH "social segregation+" OR MH "family characteristics+" OR MH "rural population+" OR MH "homeless persons+" OR

MH "work+" OR MH "occupations+" OR MH "occupational health+" OR MH "literacy+" OR MH "academic performance+" OR MH "academic success+" OR MH "education+" OR

MH "demography+" OR MH "Ethnic Groups+" OR MH "minority groups+" OR MH "Population Groups+" OR MH "refugees+" OR MH "transients and migrants+" OR MH "Race Factors+" OR MH "Race Relations+" OR MH "Continental Population Groups+")

OR

AB ("socioeconomic*" OR "socioeconomic factor*" OR "inequalit*" OR "standard of living" OR "living standard" OR "living standards" OR "high-income" OR "middle-income" OR "low-income" OR "social status" OR "social class*" OR "caste" OR "castes" OR "pay equity" OR "pay equities" OR "job ladder" OR "job ladders" OR "career ladder" OR "career ladders" OR "social development" OR "social developments" OR "social evolution" OR "socioeconomic status" OR "socioeconomic position" OR "social hierarchy" OR "social structure" OR "social structur*" OR "sociocultural*" OR "social factor" OR "social factors" OR "social marginalization" OR "working poor" OR "urban population" OR "urban population" OR "urban populations" OR "vulnerable population" OR "vulnerable population" OR "vulnerable populations" OR "social determinants of health" OR "social determinants of health" OR "health disparity" OR "health disparit*" OR "health status disparit*" OR disparity OR disparities OR inequity OR inequities OR inequality OR inequalities OR "social segregation" OR "social segregations" OR "life situation" OR "living arrangements" OR "living arrangement*" OR "family size" OR "family size*" OR "family characteristic*" OR "generation*" OR "social problem" OR "social problem*" OR "emotional deprivation" OR "social isolation*" OR "food deprivation" OR "food deprivation" OR "starvation" OR "maternal deprivation" OR "water deprivation" OR "deprivation" OR "famine*" OR "finance*" OR "financial problem*" OR

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OR "demography" OR "developing countr*" OR "ethnic group" OR "ethnic group*" OR "minority group" OR "minority group*" OR "ethnic*" "minority population*" OR "nationality" OR "nationalit*" OR "population group" OR "Race Factor*" OR "race" OR "race*" OR "racial*" OR "race relation" OR "race relation*" OR "interracial relation*" OR "ancestry group" OR "ancestry group*" OR "continental population group*")

OR

TI ("socioeconomic*" OR "socioeconomic factor*" OR "inequalit*" OR "standard of living" OR "living standard" OR "living standards" OR "high-income" OR "middle-income" OR "low-income" OR "social status" OR "social class*" OR "caste" OR "castes" OR "pay equity" OR "pay equities" OR "job ladder" OR "job ladders" OR "career ladder" OR "career ladders" OR "social development" OR "social developments" OR "social evolution" OR "socioeconomic status" OR "socioeconomic position" OR "social hierarchy" OR "social structure" OR "social structur*" OR "sociocultural*" OR "social factor" OR "social factors" OR "social marginalization" OR "working poor" OR "urban population" OR "urban population" OR "urban populations" OR "vulnerable population" OR "vulnerable population" OR "vulnerable populations" OR "social determinants of health" OR "social determinants of health" OR "health disparity" OR "health disparit*" OR "health status disparit*" OR disparity OR disparities OR inequity OR inequities OR inequality OR inequalities OR "social segregation" OR "social segregations" OR "life situation" OR "living arrangements" OR "living arrangement*" OR "family size" OR "family size*" OR "family characteristic*" OR "generation*" OR "social problem" OR "social problem*" OR "emotional deprivation" OR "social isolation*" OR "food deprivation" OR "food deprivation" OR "starvation" OR "maternal deprivation" OR "water deprivation" OR "deprivation" OR "famine*" OR "finance*" OR "financial problem*" OR

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OR "demography" OR "developing countr*" OR "ethnic group" OR "ethnic group*" OR "minority group" OR "minority group*" OR "ethnic*" "minority population*" OR "nationality" OR "nationalit*" OR "population group" OR "Race Factor*" OR "race" OR "race*" OR "racial*" OR "race relation" OR "race relation*" OR "interracial relation*" OR "ancestry group" OR "ancestry group*" OR "continental population group*")

Cochrane

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End of submission