Prevalence and incidence of multiple revisions following knee arthroplasty in Denmark 1998-2021: A nationwide population-based study
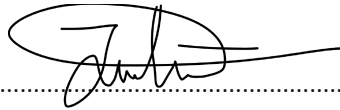
Study acronym: EMKAR

Study protocol version: Version 1.0 - 08/06/2023

SAP version number with date: Version 1.0 – 28/07/2023

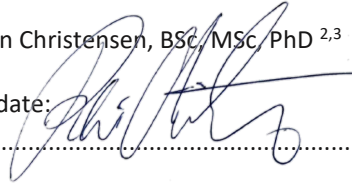**Author and statistical analyst:** Julius Tetens Hald, MD [1,2]

Signature and date: 2023, Sept 5

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Senior biostatistician: Robin Christensen, BSc, MSc, PhD [2,3]
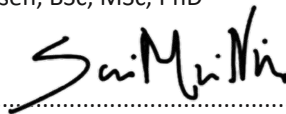
Signature and date: 2023, Sept 4.

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Signature and date: 4th of September, 2023

....

Chief investigator/clinical lead: Anders Odgaard, MD, DMSc, FRCS [1, 5]

Signature and date: 5 September 2023

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1. STUDY OVERVIEW

Background and rationale Knee arthroplasty is a common procedure performed worldwide to improve the quality of life for patients with degenerative knee conditions, trauma, and tumours. Complications can occur after knee arthroplasty, which may lead to a revision procedure, where at least one implant is exchanged, added, or removed. As the number of primary procedures in the world is increasing, so is the corresponding number of revisions. Some patients may require additional revision procedures, and some may end in a negative spiral of repeated revisions; We define three or more revisions on the same knee as being 'multiply revised'. The clinical impression of multiply revised patients is that the repeated occurrence of complications has significant impacts on the patients' quality of life including chronic pain, decreased independence, and increased morbidity. No study has yet investigated the incidence and prevalence of multiply revised knee arthroplasty patients stratified by previous revisions. To improve the care of multiply revised patients, epidemiological information is required which is the rationale of this study.

Objectives The aim of this observational study is to investigate the incidence and prevalence of multiply revised knee arthroplasty patients in all Danish patients with primary knee arthroplasty.
Hypothesis The number and burden of knee arthroplasty revision procedures and patients in Denmark has increased dramatically in the last 23 years.

Methods This is an observational study. Data will be collected from all primary and revision knee arthroplasties performed in Denmark from January 1st 1998 to 31st December 2021. Data will be acquired from two registers: The Danish Knee Arthroplasty Register (DKR), containing surgeon-reported data on primary and revision knee arthroplasties. In addition, data will be acquired from Landspatientregisteret, which contains all clinical data collected during any visit to a public or private healthcare facility in Denmark.

PICOTS

Population: All Danish citizens who have received a primary knee arthroplasty at a Danish healthcare facility, from the 1st of January 1998 the to 31st of December 2021

Intervention/Exposure Multiple revision knee arthroplasties in the same knee

Comparator: None

Outcome (primary): Annual standardized prevalence and incidence of n-grade revisions following knee arthroplasty between 1998 and 2021 in Denmark.

Time: Retrospectively, from the 1st of January 1998 to the 31st of December 2021, i.e., up to 24 years follow-up.

Study design: Observational retrospective register study.

Further statistical details

Power considerations: A sample size calculation has not been performed, as our sample will be determined solely by the actual number of eligible patients available from the registries.

Framework: This is an observational study aimed at reporting the prevalence and incidence of multiple revised knee arthroplasty patients in Denmark. No formal statistical testing will be performed.

Statistical interim analyses and stopping guidance: Not applicable.

Timing of final analysis: Access to all data has been acquired. The final analysis will be performed after the completion and acceptance of the SAP by all participants.

Timing of outcome assessment: (see next section).

Confidence intervals and P values: Not applicable.

Multiplicity: No formal statistical testing will be performed.

Statistical software: R, version 4.3.0 (or newer).

2. TABULAR PRESENTATION OF TIMING OF OUTCOME MEASUREMENTS

Registry	Observation period	Variables relevant for this study
The Danish Knee Arthroplasty Register	January 1st 1998 – 31st December 2021	ID-key (number)
		Date of surgery (date)
		Code for implant type (number)
		Revision performed (yes/no)
		Revision of tibial component (yes/no)
		Revision of femoral component (yes/no)
		Laterality (left/right)
		Sex (male/female)
		Age (number)
		Indication for primary procedure (number)
		Performing institution (number)
		Duration of procedure (minutes)
Landspatientregisteret	January 1st 1998 – 31st December 2021	ID-key (number)
		Date of surgery (date)
		Code for procedure (number)
		Laterality (left/right)
		Sex (male/female)
		Age (number)
		Performing institution (number)
		Year of death or emigration (date)

3. ELABORATIONS ON OUTCOMES AND DATA

Data management, The Danish Knee Arthroplasty Register:

ID-key: unique identification key specifying patient. This key is an anonymized ID key in encrypted integer format, and hence, is **not** equal to the CPR number of the participants.

Date of surgery: The date that the procedure took place. In character (date) format.

Code for implant type

For the Danish knee arthroplasty register a set of codes are used to specify the inserted implant.

Primary procedures are defined as the following codes:

    1 = TKA
    2 = medial UKA
    3= lateral UKA
    4 = patellofemoral UKA
    5+7 = rotating hinge-prosthesis
    6 = Resection prosthesis
    9 = Partial resurfacing
    100 = Rotating hinge-prosthesis with condyle resection
    104 = Resection or segmental prosthesis
    105 = Hemicap
    107 = Episealer
    119 = tibiaprosthesis w. stem

Revision procedure performed:

If the procedure is a revision it is marked with yes, otherwise it is marked with no.

Definition of major revision:

A revision in DKR is defined as a major revision, if either the femoral or the tibial component has been revised. A procedure is marked as a major revision if either one of the variables "Revision of tibial component" and/or "revision of femoral component" are marked as yes.

Definition of major and minor revision

Major and minor revisions are defined as the following implant types:

    1 = TKA
    2 = medial UKA
    3= lateral UKA
    4 = patellofemoral UKA
    5+7 = rotating hinge-prosthesis
    6 = Resection prosthesis
    9 = Partial resurfacing
    10 = articulated cement spacer
    11 = fixated cement spacer
    100 = Rotating hinge-prosthesis with condyle resection
    103 = Removal of patella component
    104 = Resection or segmental prosthesis
    105 = Hemicap
    107 = Episealer
    108 = Other removal
    109 = New liner
    110 = New patella component
    112 = Exchange of femoral component

117 = Removal of tibia component
119 = Insertion of stemmed tibia component
120 = Exchange of tibia component

Laterality: Code for specifying right/left knee. 1 = right, 2 = left

Sex: Specifying the sex of the patient. M = male, F = female

Age: Number specifying the age of the patient at the time of performed procedure

Indication for primary procedure: Code specifying the indication for performing the primary procedure. The codes are:

    1 = Idiopathic knee osteoarthritis
    2 = Secondary arthritis
    3 = Sequelae after tibia condyle fracture
    4 = Sequelae after femur condyle fracture
    5 = sequelae after patella fracture
    6 = Rheumatoid arthritis
    7 = Sequelae after other arthritis
    8 = Haemophilia
    9 = Tumour - primary
    10 = Tumour – metastasis

Performing institution: Code specifying the performing institution. The codes are classified as SHAK-codes, developed by "Sundhedsdatastyrelsen". (https://medinfo.dk/sks/brows.php)

Duration of procedure: Number specifying the duration of the performed procedure. Given as minutes.

Data management, Landspatientregisteret:
ID-key: unique identification key specifying patient. This key is an anonymized ID key in character format, and hence, is **not** equal to the CPR-number of the participants.

Date of surgery: The date that the procedure took place. In character (date) format.

Code for procedure: NOMESCO procedure codes are used in Landspatientregisteret. KNGB* codes specify primary procedures, whereas KNGC* codes specify revision procedures.

Definition of major revisions in Landspatientregisteret

Revision procedures are marked with KNGC* codes. The following KNGC codes define a major revision:

KNGC01: Secondary insertion of proximal component of uncemented partial prosthesis in knee
KNGC02: Secondary insertion of distal component of uncemented partial prosthesis in knee
KNGC03: Secondary insertion of patellofemoral component of uncemented partial prosthesis in knee
KNGC04: Secondary insertion of multiple components of uncemented partial prosthesis in knee
KNGC11: Secondary insertion of proximal component of cemented partial prosthesis in knee
KNGC12: Secondary insertion of distal component of cemented partial prosthesis in knee
KNGC13: Secondary insertion of patellofemoral component of cemented partial prosthesis in knee
KNGC14: Secondary insertion of multiple components of cemented prosthesis in knee
KNGC19: Secondary insertion of cemented partial prosthesis in knee without specification
KNGC20: Secondary insertion of all components in uncemented total prosthesis in knee
KNGC21: Secondary insertion of proximal component in uncemented total prosthesis in knee
KNGC22: Secondary insertion of distal component in uncemented total prosthesis in knee
KNGC24: Secondary insertion of multiple components un uncemented total prosthesis in knee
KNGC29: Secondary insertion of uncemented total prosthesis in knee without specification

KNGC30: Secondary insertion of all components of hybrid total prosthesis in knee
KNGC31: Secondary insertion of proximal component of hybrid total prosthesis in knee
KNGC32: Secondary insertion of distal component of hybrid total prosthesis in knee
KNGC34: Secondary insertion of more than one component of hybrid total prosthesis in knee
KNGC39: Secondary insertion of hybrid total prosthesis in knee without specification
KNGC40: Secondary insertion of all components of cemented total prosthesis in knee
KNGC41: Secondary insertion of proximal component of cemented total prosthesis in knee
KNGC42: Secondary insertion of distal component of cemented total prosthesis in knee
KNGC44: Secondary insertion of multiple components of cemented total prosthesis in knee
KNGC49: Secondary insertion of cemented total prosthesis in knee without specification
KNGC99: Other secondary insertion of prosthesis in knee

Definition of minor revisions in Landspatientregisteret
Minor revisions are defined as the KNGC codes listed here:

KNGC02A: Secondary insertion of only polyethylene liner in uncemented partial prosthesis in knee
KNGC09: Secondary insertion of uncemented partial prosthesis in knee without specification
KNGC1: Secondary insertion of cemented partial prosthesis in knee
KNGC12A: Secondary insertion of only polyethylene liner in cemented partial prosthesis in knee
KNGC22A: Secondary insertion of only polyethylene liner in uncemented total prosthesis in knee
KNGC23: Secondary insertion of patellofemoral component in uncemented total prosthesis in knee
KNGC32A: Secondary insertion of only polyethylene liner in hybrid total prosthesis in knee
KNGC33: Secondary insertion of patellofemoral component in hybrid total prosthesis in knee
KNGC42A: Secondary insertion of only polyethylene liner in hybrid total prosthesis in knee
KNGC43: Secondary insertion of patellofemoral component of cemented total prosthesis in knee
KNGC59: Secondary insertion of interpolated prosthesis in knee
KNGC59A: Insertion of spacer in knee in connection with revision
KNGC99A: Secondary insertion of patella component
KNGS49: Incision or revision with placement of medication in case of infection in knee joint

Laterality: Code for specifying right/left knee. TUL1 = right, TUL2 = left

Sex: Specifying the sex of the patient. M = male, F = female

Age: Number specifying the age of the patient at the time of the performed procedure

Performing institution: Code specifying the performing institution. The codes are classified as SHAK-codes, developed by "Sundhedsdatastyrelsen". (https://medinfo.dk/sks/brows.php)

Year of death: The year in which the patient has died. The patient will be marked as "ALIVE" if death has not occurred at the end of the observation period.

Data management, for both registers.

Definition of a revision: A revision is defined as the exchange, addition, or removal of a knee prosthesis component (1). However, knee arthrodesis and amputation are not included in this study.

Definition of major revision: A major revision is defined as exchange of the femoral component and/or the tibial component with subgroups of tibial, femoral and all component exchange (2).

Definition of minor revision: A minor revision is defined as the exchange of polyethylene liner and/or addition or revision of the patella component. Insertion/removal/exchange of spacers are also included in this category (2).

<u>Population:</u> The population is defined as the number of alive citizens in the state of Denmark. Annual populations are defined as the population in Denmark on the 1st of January that year. Additional data for sex and age of the population is acquired. Data for the population is acquired from Danmarks Statistik (3).

<u>In case of disagreement between registers:</u> In cases of discrepancy between the two registers, Landspatientregisteret will overrule the Danish Knee arthroplasty register concerning following variables:
Laterality
Date of surgery
Gender
Age
Performing institution

In cases of discrepancy between the two registers, the Danish Knee arthroplasty register will overrule Landspatientregisteret concerning following variables:
Procedure code
Revision of tibia
Revision of femur
Indication

<u>Calculation of standardized prevalence:</u> Annual standardized prevalence is calculated as the number of patients living with a n-grade revision during a given year as a proportion of the population in Denmark (the 1st of January that year) (3). The prevalence is then multiplicated by 100,000 for standardization. This is done for each level of revision, each year. E.g., the standardized prevalence for 1998 is calculated as:

$$Standardized\ prevalence, 1998 = \frac{Number\ of\ knees\ living\ in\ 1998\ with\ a\ n-grade\ revision}{Total\ population\ in\ Denmark\ in\ 1998} * 100,000$$

The prevalence is only calculated for revisions performed between January 1st 1998 and December 31st 2021.

<u>Calculation of standardized incidence:</u> Annual standardized incidence is calculated as the number of new n-grade revisions performed as a proportion of the population in Denmark during a specific year. The population size of Denmark is defined as the population size at January 1st for that year (3). The incidence is then multiplicated by 100,000 for standardization. This is done for each level of revision, each year. E.g., the standardized incidence for 1998 is calculated as:

$$Standardized\ incidence, 1998 = \frac{Number\ of\ new\ n-grade\ revisions\ in\ the\ population\ in\ 1998}{Total\ population\ in\ Denmark\ in\ 1998} * 100,000$$

<u>Missing data:</u> We expect to encounter some missing data. All missing data will be described.

Data validation:
All variables used in the analysis will be checked for obvious outliers and inconsistencies.

Data template:
Based on this SAP, the statistical analyst will develop a tailored data template illustrating the data structure required for the statistical analyses.

4. PROTOCOL DEVIATIONS WITH BEARING ON THIS STATISTICAL ANALYSIS PLAN

The following details in this SAP represent deviations from the protocol.

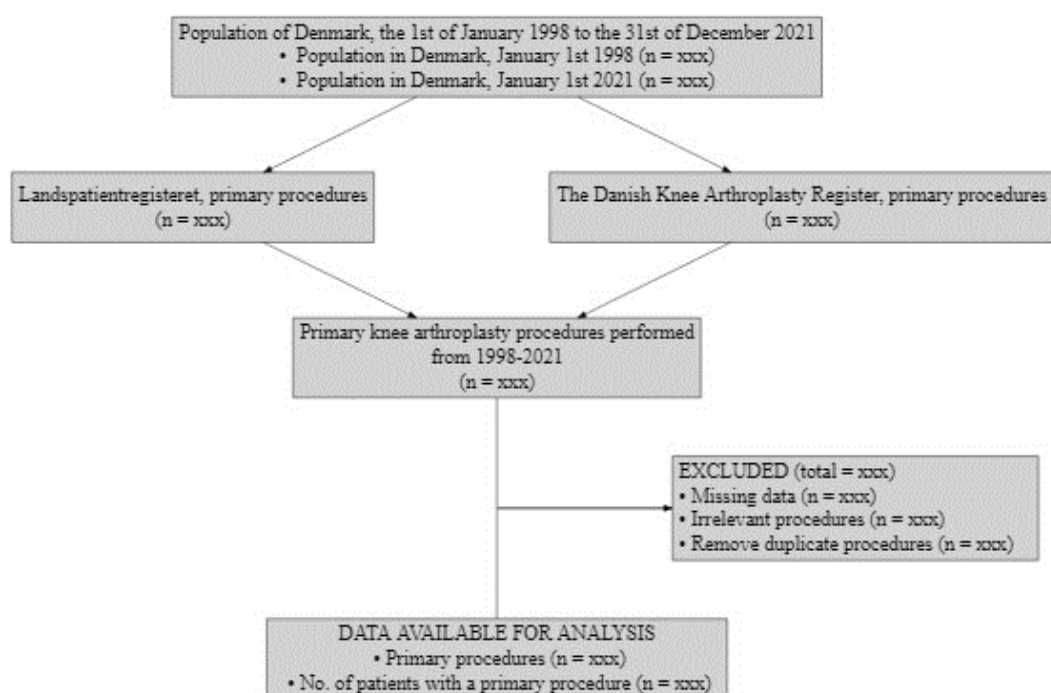| Header in the protocol	Change	Reason
(currently no deviations)		

5. OUTLINE

The anticipated (predefined) outline of the manuscript is illustrated below.

Figure 1. Flow diagram
Anticipated plot design, illustrating potential reasons for exclusion:

Population of Denmark, the 1st of January 1998 to the 31st of December 2021
- Population in Denmark, January 1st 1998 (n = xxx)
- Population in Denmark, January 1st 2021 (n = xxx)

Landspatientregisteret, primary procedures
(n = xxx)

The Danish Knee Arthroplasty Register, primary procedures
(n = xxx)

Primary knee arthroplasty procedures performed
from 1998-2021
(n = xxx)

EXCLUDED (total = xxx)
- Missing data (n = xxx)
- Irrelevant procedures (n = xxx)
- Remove duplicate procedures (n = xxx)

DATA AVAILABLE FOR ANALYSIS
- Primary procedures (n = xxx)
- No. of patients with a primary procedure (n = xxx)

Table 1. Characteristics of primary knee arthroplasty procedures.

Characteristics	Primary knee arthroplasties (n =)
Age, years	
Females, n (%)	
Implant type, n (%)	
- TKA	
- Medial UKA	
- Lateral UKA	
- Patellofemoral UKA	
- Unspecified UKA	
- Rotating hinge prosthesis	
- Rotating hinge prosthesis with condyle resection	
- Resection prosthesis	
- Partial resurfacing	
- Unspecified implant type (KNGB09, KNGB14, KNGB99)	
- Isolated patella	
Region for the procedure, n (%)	
- Northern Region of Denmark	
- Middle Region of Denmark	
- Southern Region of Denmark	
- Zealand Region of Denmark	
- Capital Region of Denmark	
- Private hospitals	
- Unknown	
Indication for the primary procedure, n (%)	
- Idiopathic knee osteoarthritis	
- Secondary knee osteoarthritis	
- Sequelae following tibia condyle fracture	
- Sequelae following femur condyle fracture	
- Sequelae following patella fracture	
- Rheumatoid arthritis	
- Sequelae following other arthritis	
- Haemophilia	
- Primary bone tumour	
- Metastatic bone tumour	
- Unknown	
Duration of the procedure, minutes	

Values are means (SD) unless otherwise stated.
Abbreviations: TKA = total knee arthroplasty. UKA = unicompartmental knee arthroplasty

Further statistical information related to table 1:

Data will be presented as mean with standard deviation (SD) when normally distributed or as median with interquartile range in case of skewed data. Dichotomous and categorical data will be presented in proportions. Normality of the data will be assessed using Q-Q plots, and histograms.

Table 2. Annual occurrence of primary procedures and major n-grade revisions.

Year	Primary procedures, n	1st revision, n	2nd revision, n	....	n grade revision, n	Maximal grade of revision performed*
1998						
1999						
2000						
2001						
2002						
2003						
2004						
2005						
2006						
2007						
2008						
2009						
2010						
2011						
2012						
2013						
2014						
2015						
2016						
2017						
2018						
2019						
2020						
2021						

Only grades of revisions with occurrences >10 are shown
*The maximal grade of revision performed is defined as the single greatest grade of revision performed that year

Table 3: Annual occurrence of all n-grade revisions (including both major and minor revisions).
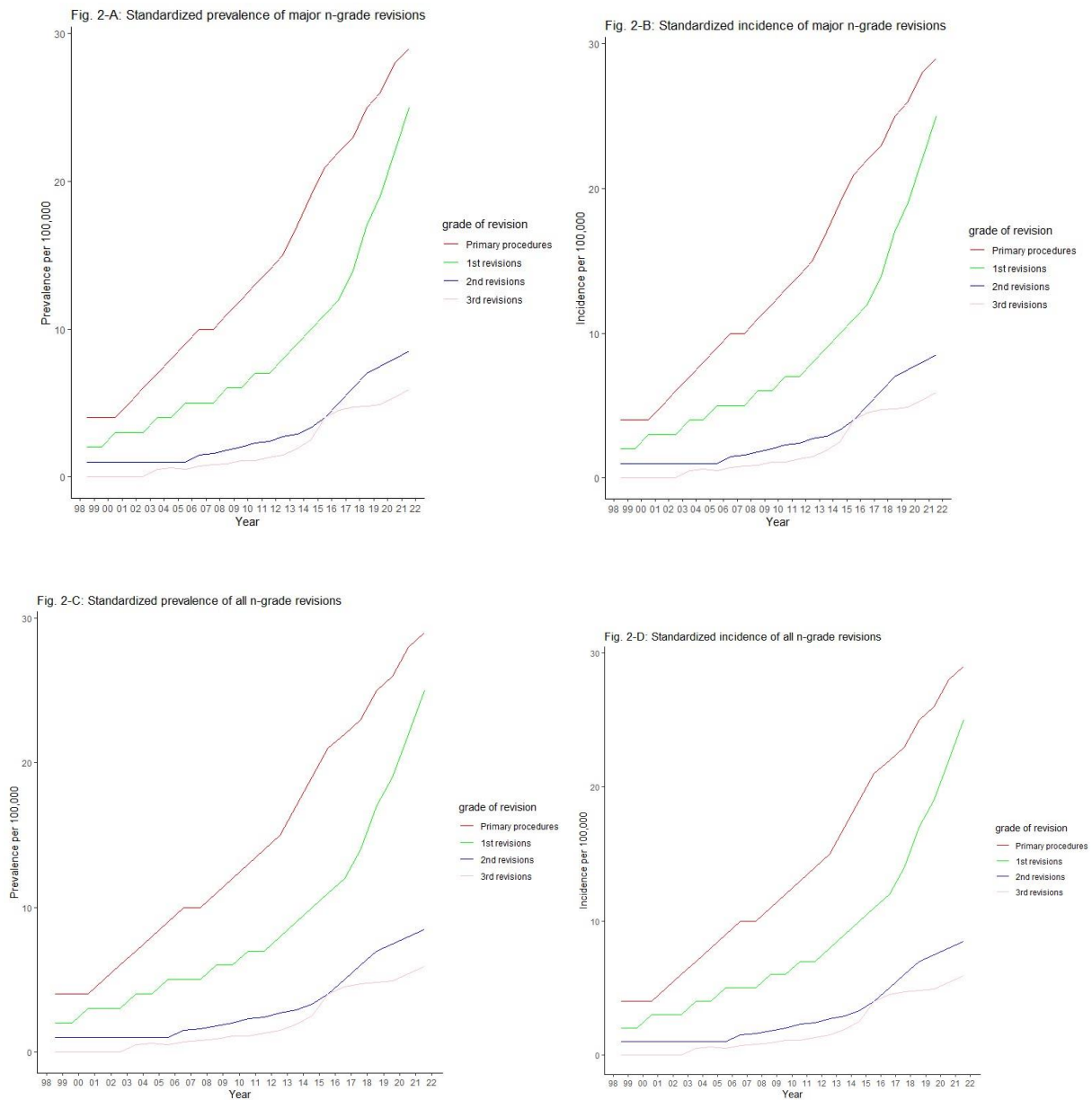
Year	1st revision	2nd revision	....	n grade revision	Maximal grade of revision performed*
1998					
1999					
2000					
2001					
2002					
2003					
2004					
2005					
2006					
2007					
2008					
2009					
2010					
2011					
2012					
2013					
2014					
2015					
2016					
2017					
2018					
2019					
2020					
2021					

Only grades of revisions with occurrences >10 for all years are shown
*The maximal grade of revision performed is defined as the single greatest grade of revision performed that year

Figure 2. The standardized prevalence and incidence rates of n-grade revisions from 1998 to 2021.

Anticipated plot design, illustrating with imaginary data, A-D

Fig. 2-A: Standardized prevalence of major n-grade revisions

Fig. 2-B: Standardized incidence of major n-grade revisions

Fig. 2-C: Standardized prevalence of all n-grade revisions

Fig. 2-D: Standardized incidence of all n-grade revisions

Panel A and B illustrates standardized prevalence and incidence of <u>major</u> n-grade revisions. Panel C and D illustrate standardized prevalence and incidence of <u>*all*</u> n-grade revisions (including both major and minor revisions). Only grades of revisions with occurrences >10 are shown; for prevalence, >n-grade revisions are reported as well.

Figure 3. The standardized prevalence of patients with their total sum of revisions.
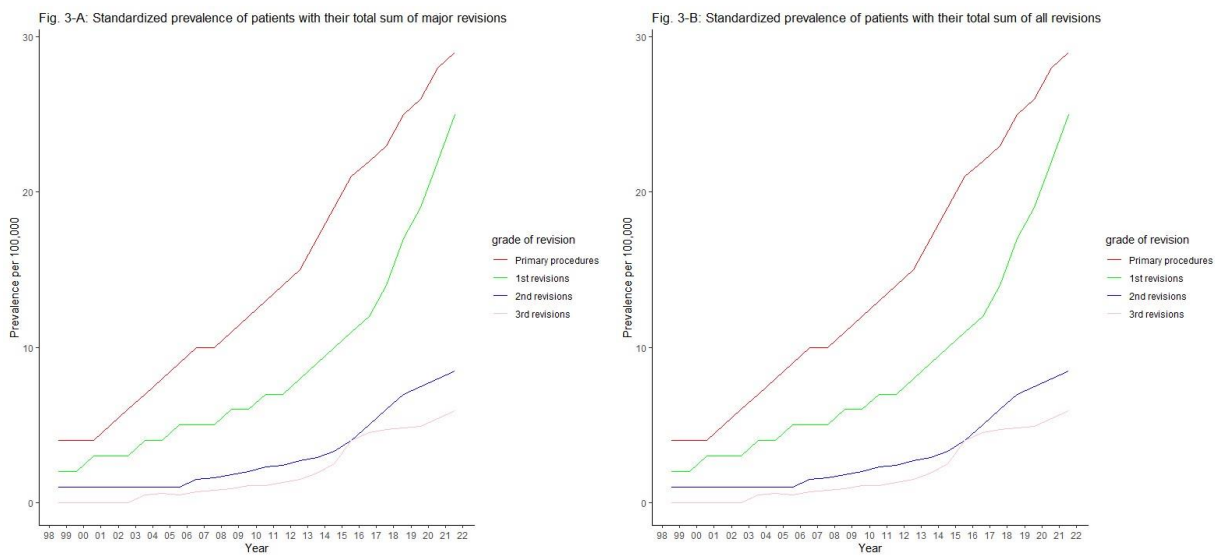
Panel A illustrates standardized prevalence of patients with major n-grade revisions. Panel B illustrates standardized prevalence rates of patients with all n-grade revisions (including major and minor revisions).
The total sum of revisions is the summation of all revision procedures performed on a patient. E.g., a patient with 3 revisions performed on one knee and 4 revisions performed on the other knee, is categorized as a 7-grade revision patient. Only grades of revisions with occurrences >10 are shown as well as >n-grade grade revisions.

SUPPLEMENTARY MATERIAL

The anticipated (predefined) supplementary material of the manuscript is illustrated below.
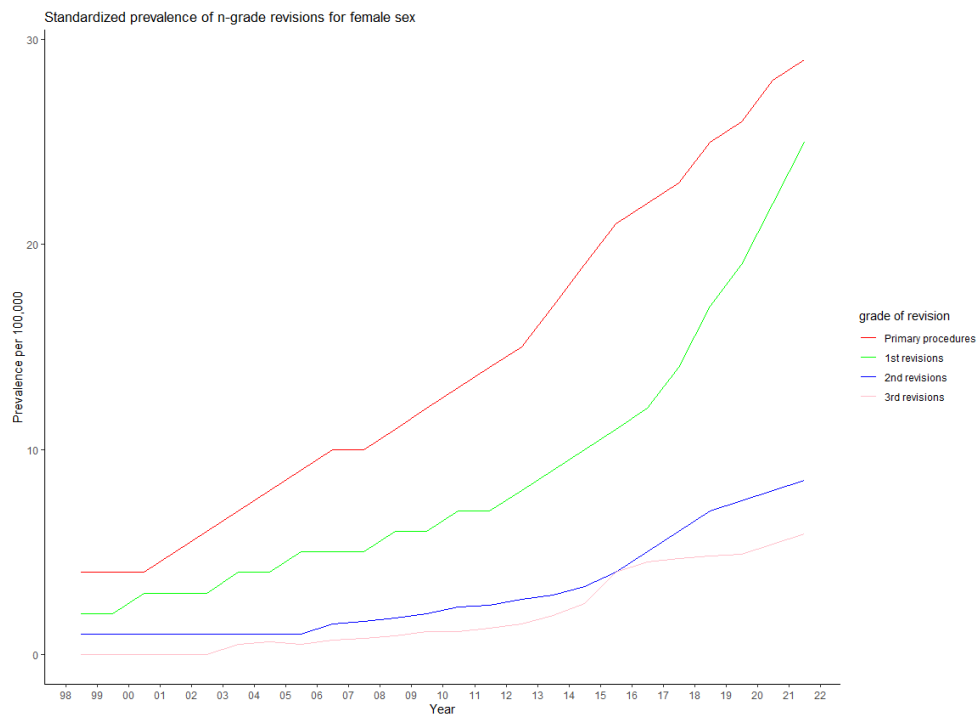
Supplementary file 1. Protocol

Supplementary file 2. This SAP

Supplementary Figure 1. Standardized annual prevalence (panel A) and incidence rates (panel B) for major n-grade revisions for male sex
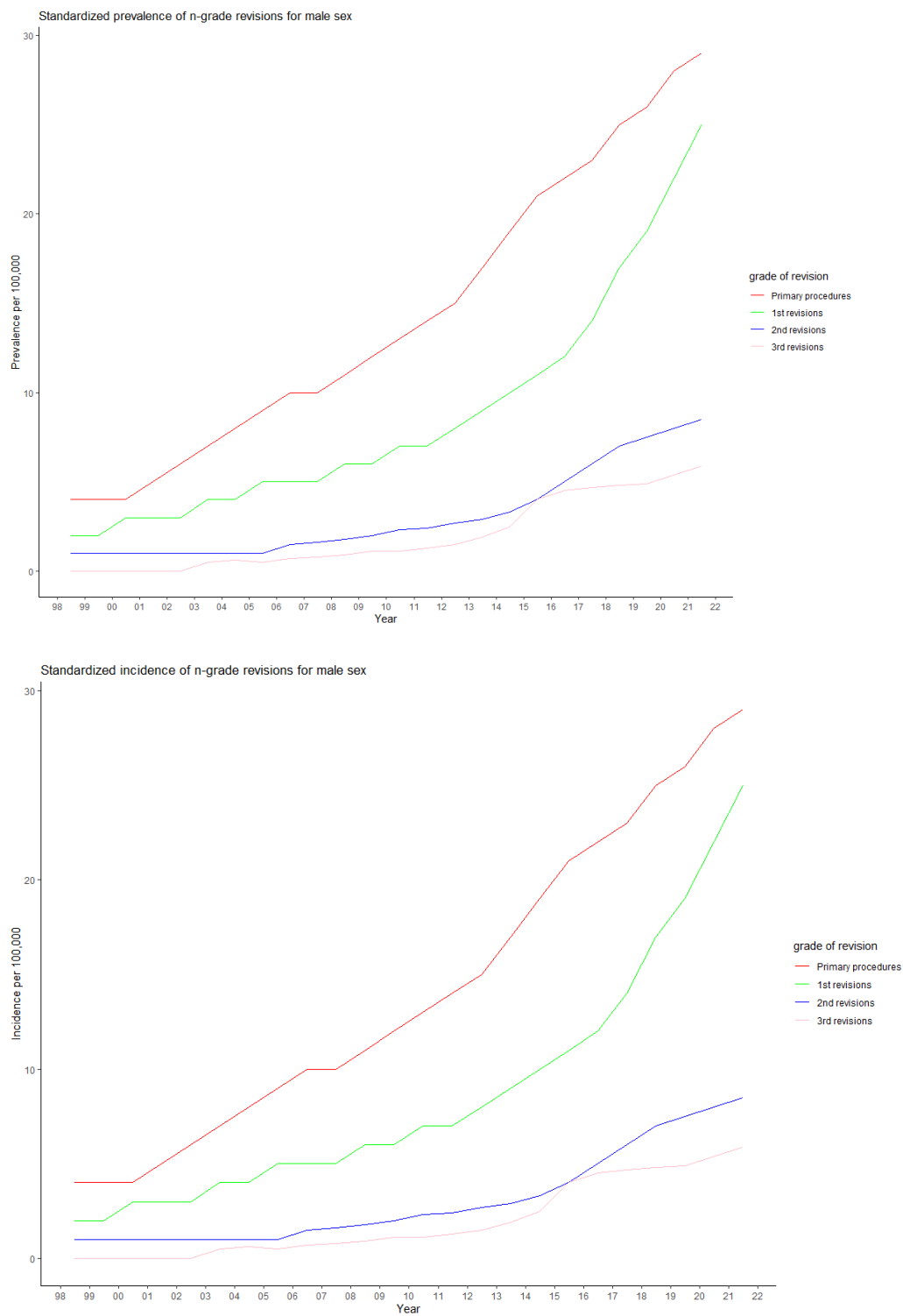
Only grades of revisions with occurrences >10 are shown; for prevalence, >n grade are reported as well.
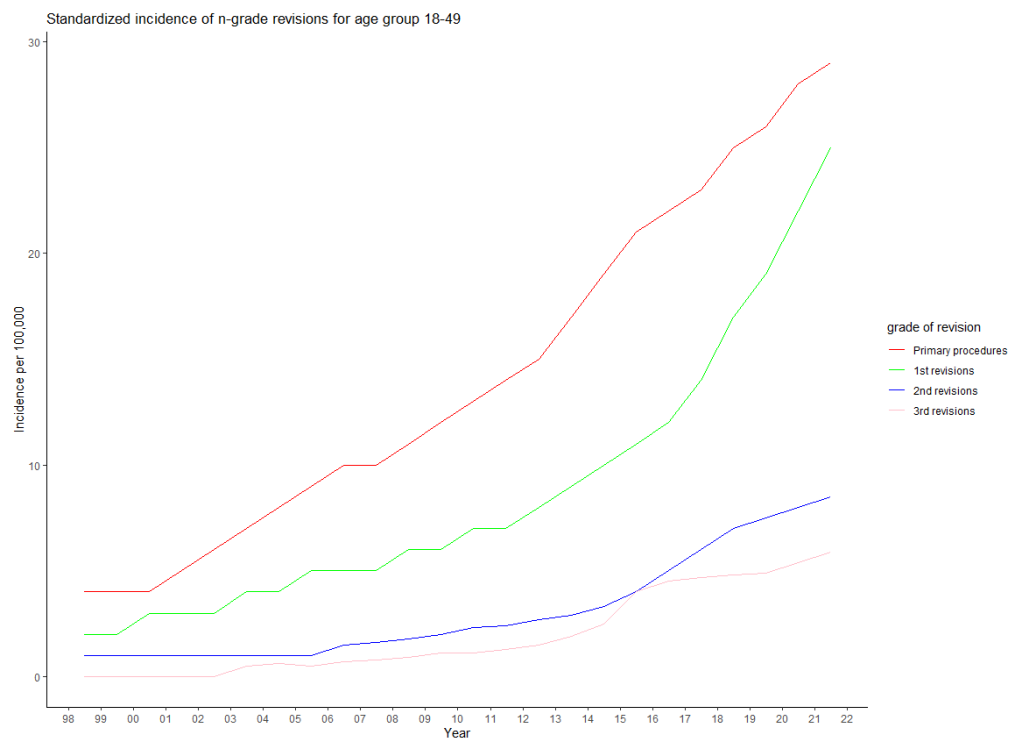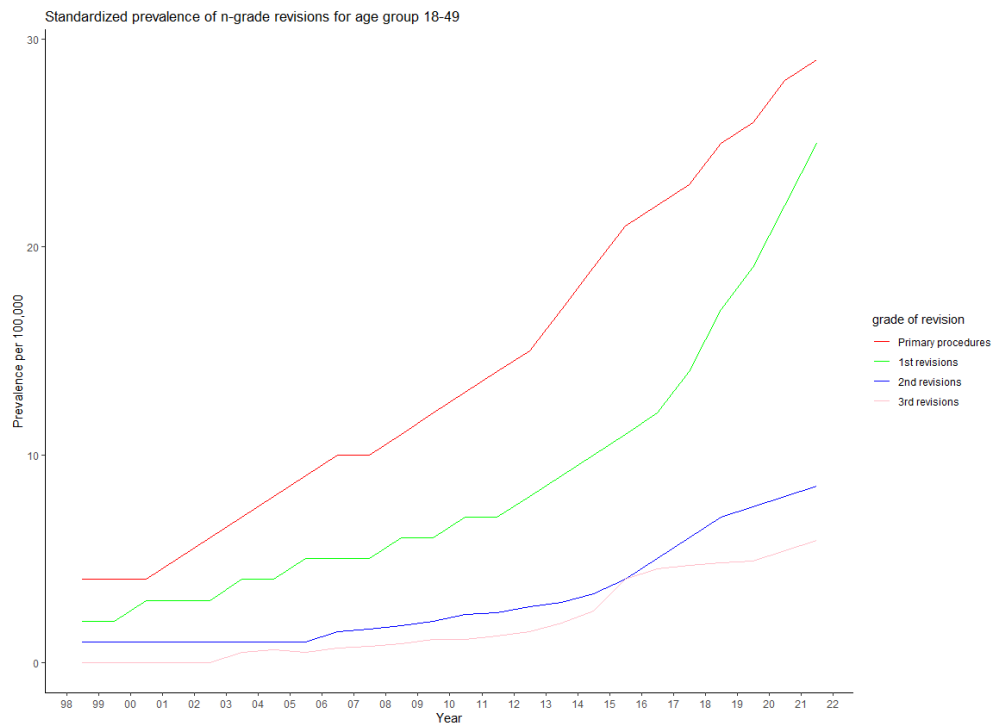
Supplementary Figure 2. Standardized annual prevalence (panel A) and incidence rates (panel B) for major n-grade revisions for <u>female sex</u>.

Standardized prevalence of n-grade revisions for female sex

Standardized incidence of n-grade revisions for female sex
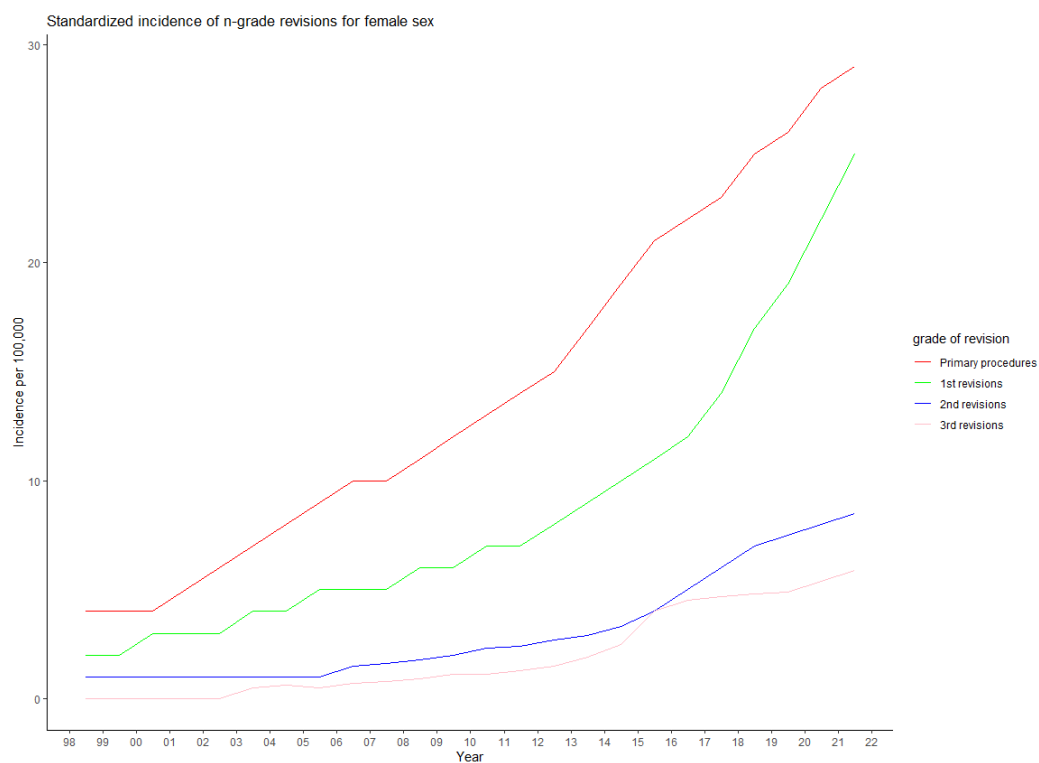
Only grades of revisions with occurrences >10 are shown; for prevalence, >n grade are reported as well.
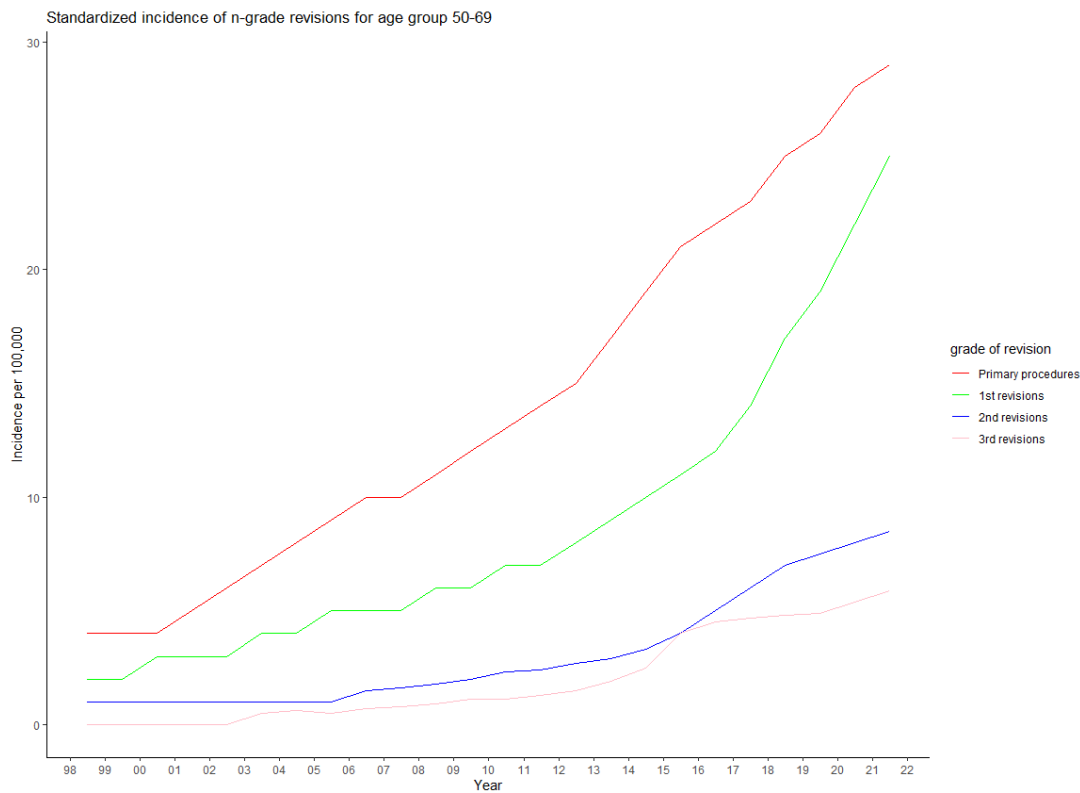
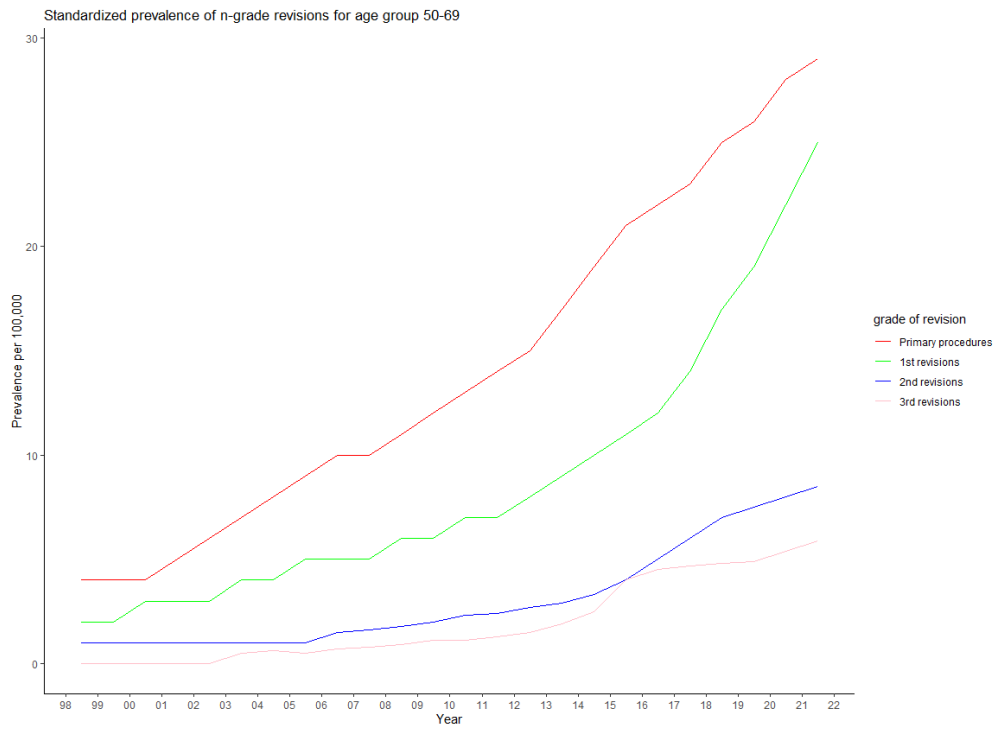**Supplementary Figure 3:** Standardized annual prevalence (panel A) and incidence rates (panel B) for major n-grade revisions for <u>age group 18-49.</u>

Standardized prevalence of n-grade revisions for age group 18-49

Standardized incidence of n-grade revisions for age group 18-49
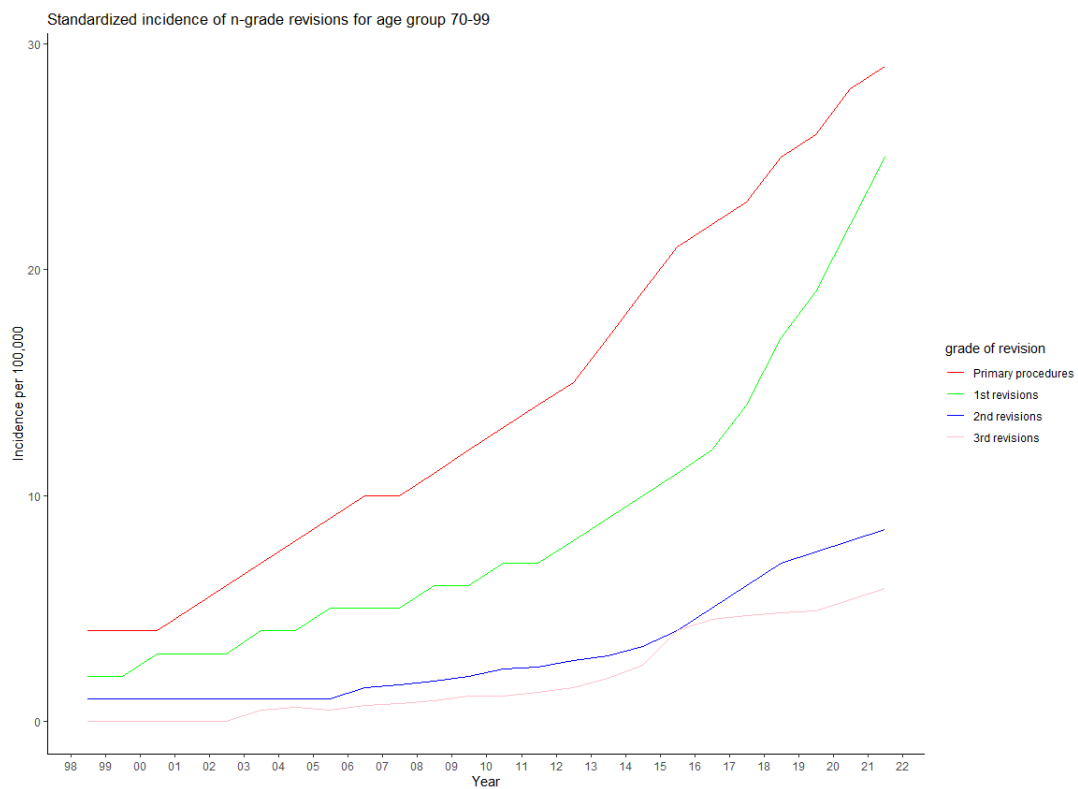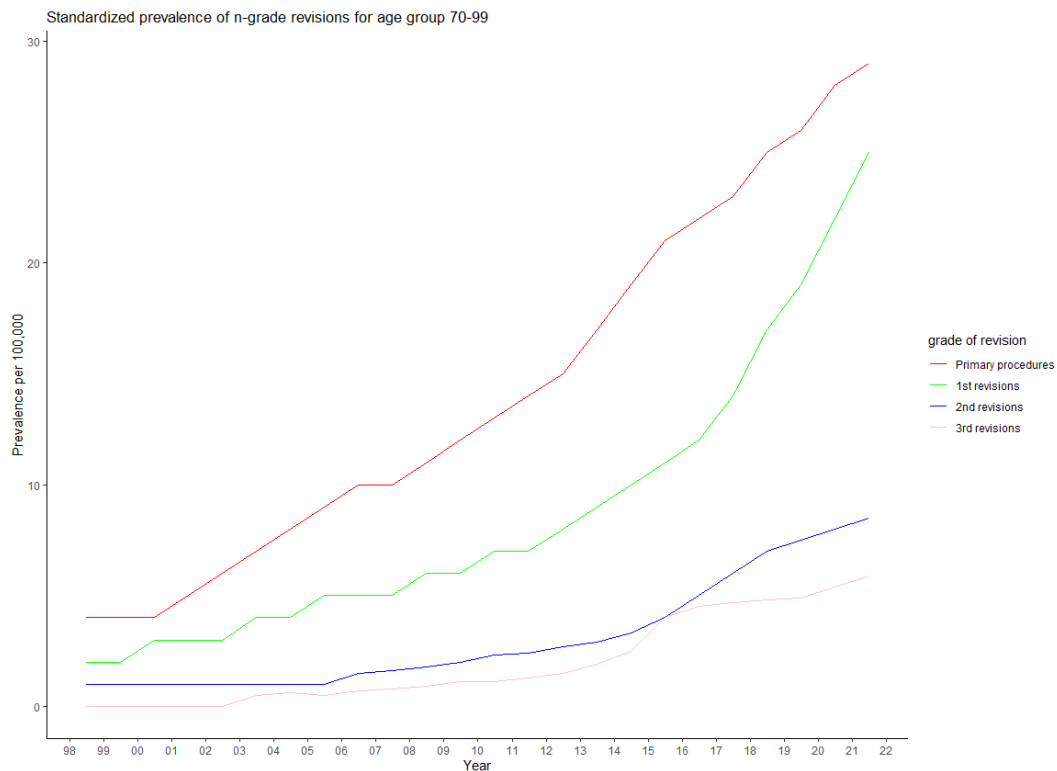
Only grades of revisions with occurrences >10 are shown; for prevalence, >n grade are reported as well.

Supplementary Figure 4: Standardized annual prevalence (panel A) and incidence rates (panel B) for major n-grade revisions for <u>age group 50-69</u>.

Standardized prevalence of n-grade revisions for age group 50-69

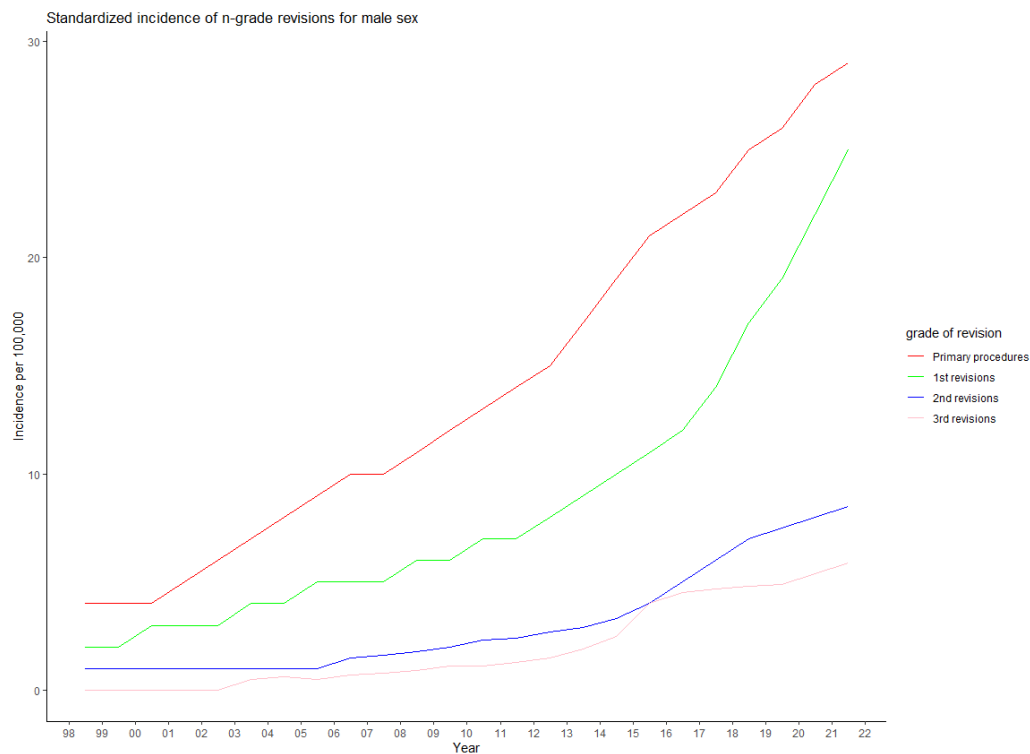Standardized incidence of n-grade revisions for age group 50-69

Only grades of revisions with occurrences >10 are shown; for prevalence, >n grade are reported as well.

Supplementary Figure 5. Standardized annual prevalence (panel A) and incidence rates (panel B) for major n-grade revisions for <u>age group 70-99.</u>

Standardized prevalence of n-grade revisions for age group 70-99

Standardized incidence of n-grade revisions for age group 70-99
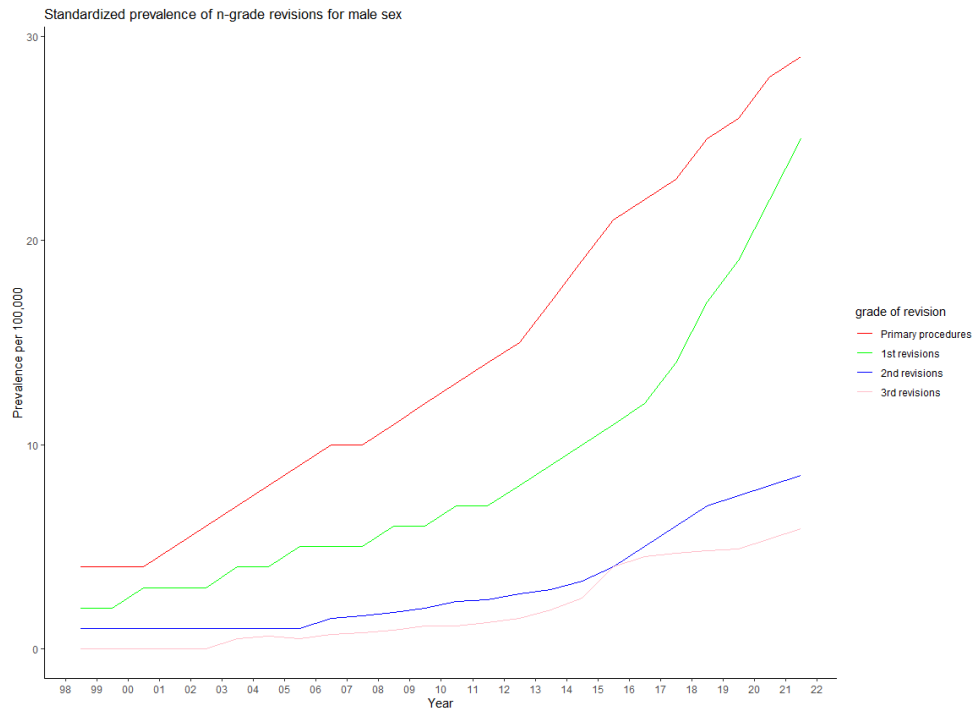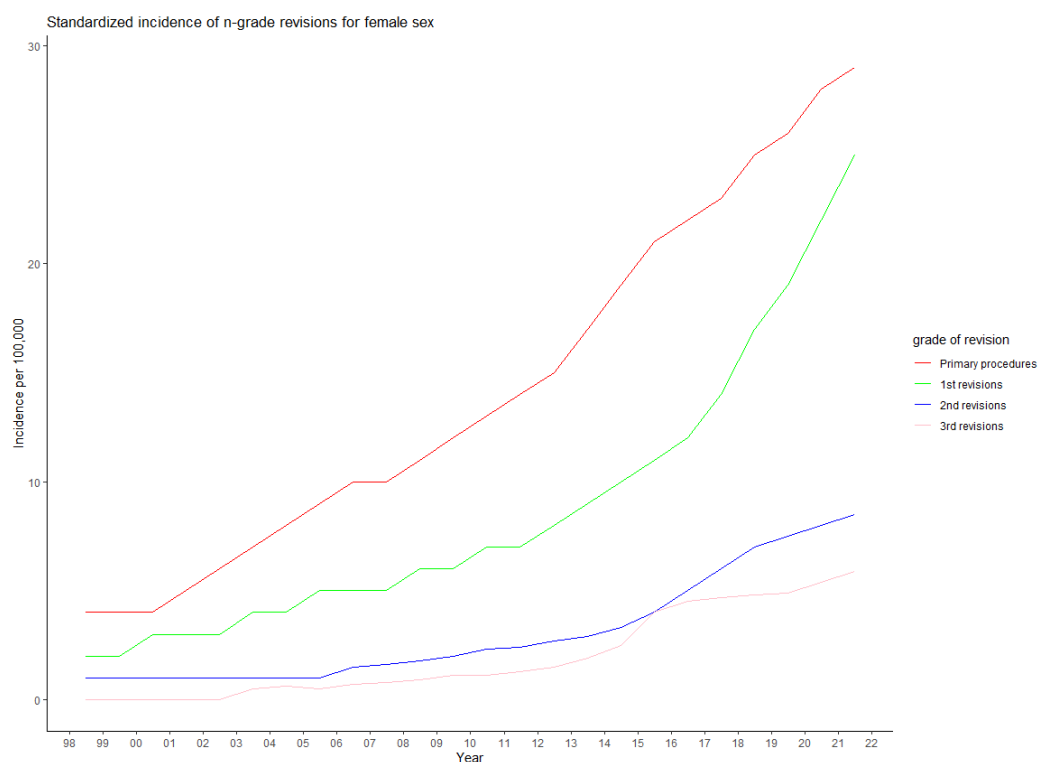
Only grades of revisions with occurrences >10 are shown; for prevalence, >n grade are reported as well.

Supplementary Figure 6: Standardized annual prevalence (panel A) and incidence rates (panel B) for all n-grade revisions (including major and minor revisions) for <u>male sex</u>.

Only grades of revisions with occurrences >10 are shown; for prevalence, >n grade are reported as well.

Supplementary Figure 7: Standardized annual prevalence (panel A) and incidence rates (panel B) for all n-grade revisions (including major and minor revisions) for <u>female sex</u>.

Standardized prevalence of n-grade revisions for female sex

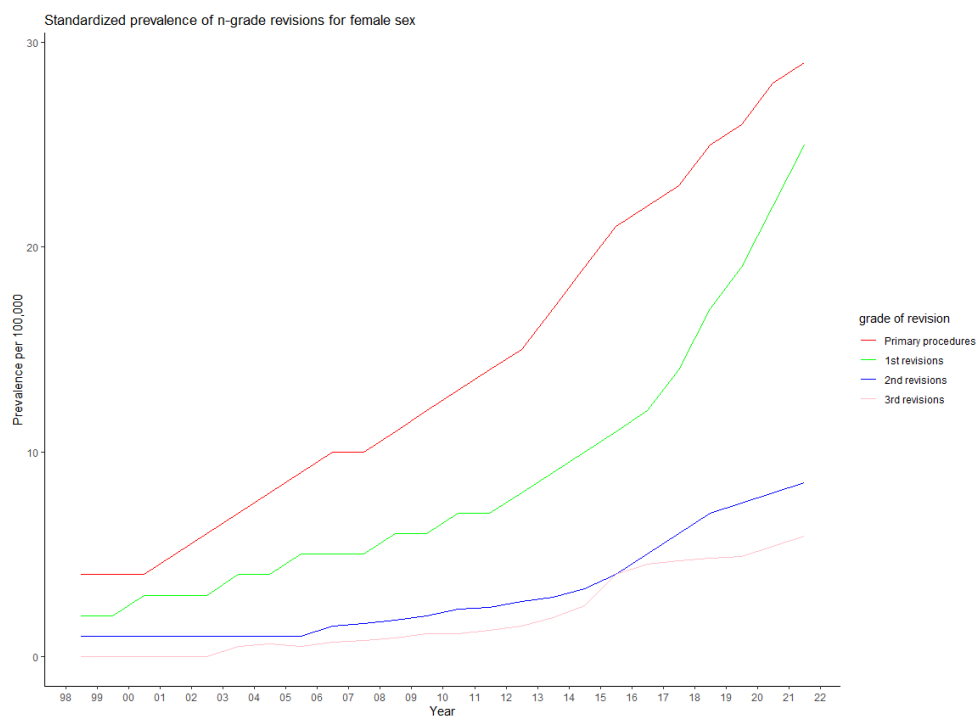Standardized incidence of n-grade revisions for female sex

Only grades of revisions with occurrences >10 are shown; for prevalence, >n grade are reported as well.

Supplementary Figure 8: Standardized annual prevalence (panel A) and incidence rates (panel B) for all n-grade revisions (including major and minor revisions) for age group 18-49.
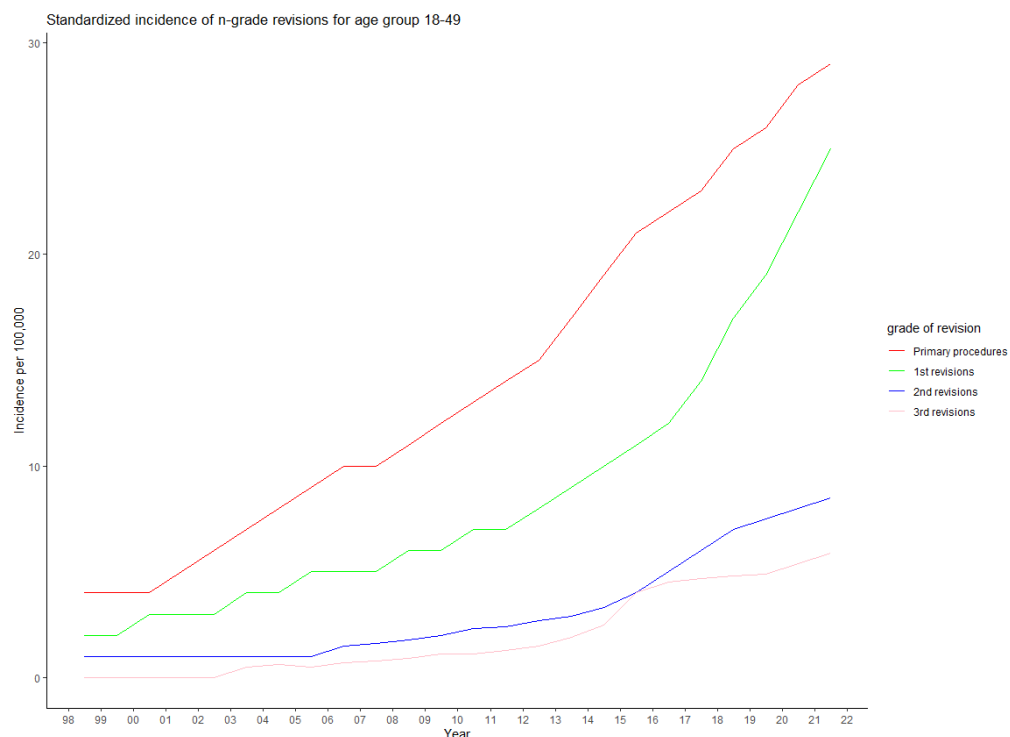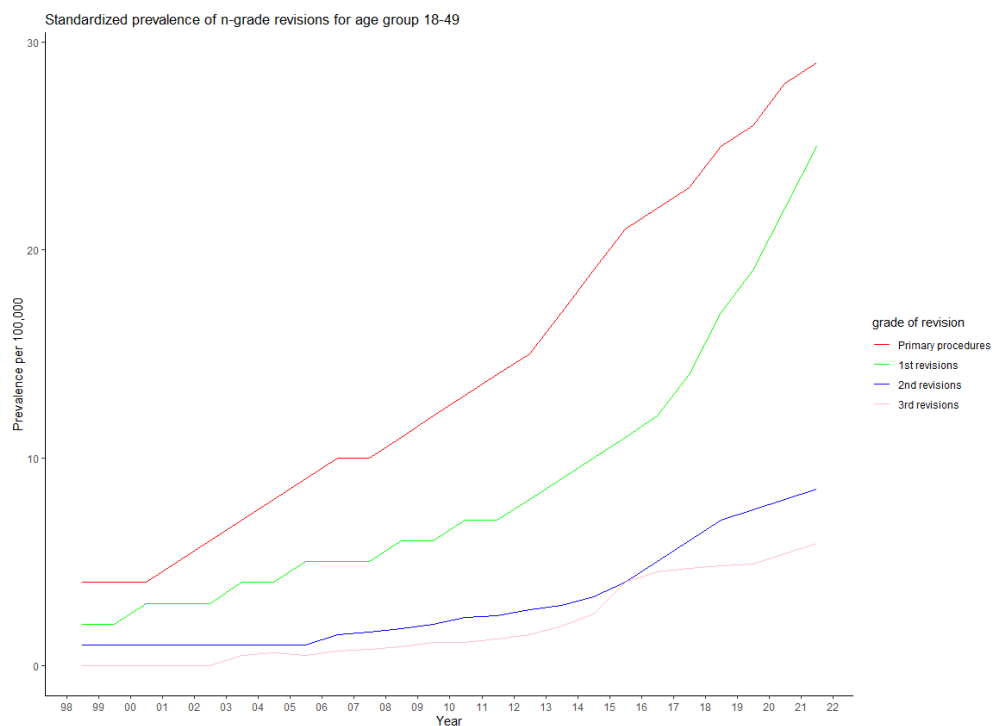

Only grades of revisions with occurrences >10 are shown; for prevalence, >n grade are reported as well.

Supplementary Figure 9: Standardized annual prevalence (panel A) and incidence rates (panel B) for all n-grade revisions (including major and minor revisions) for <u>age group 50-69.</u>

Standardized prevalence of n-grade revisions for age group 50-69

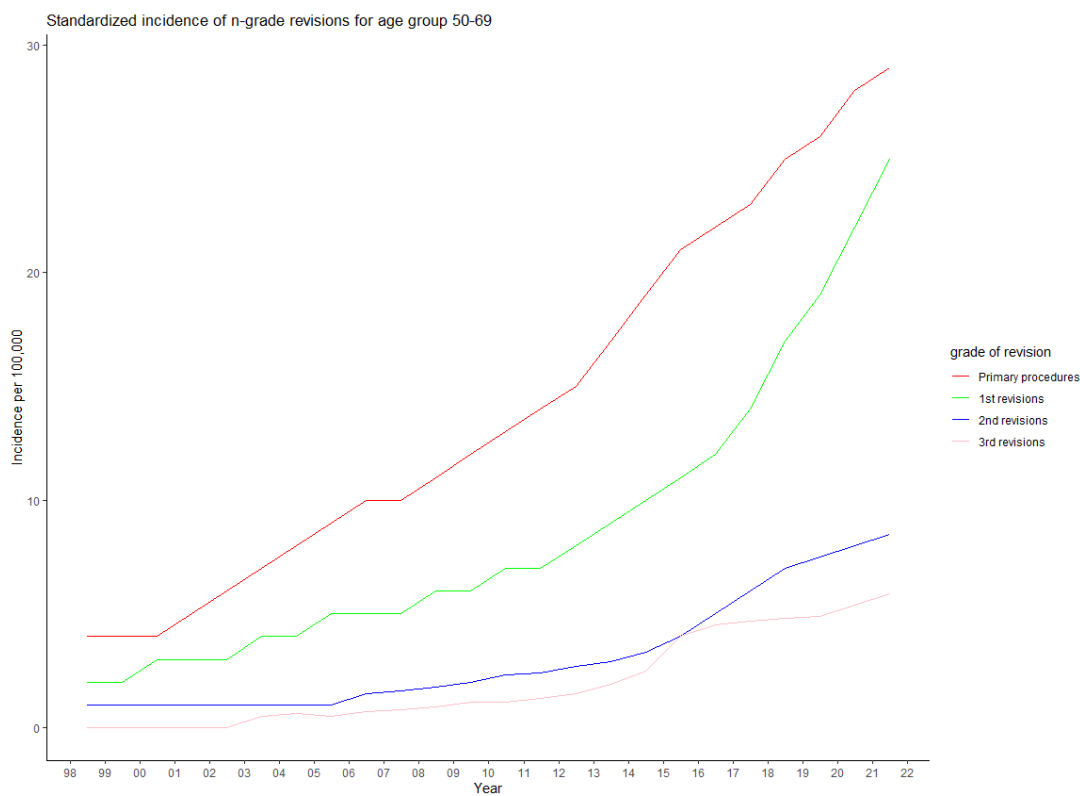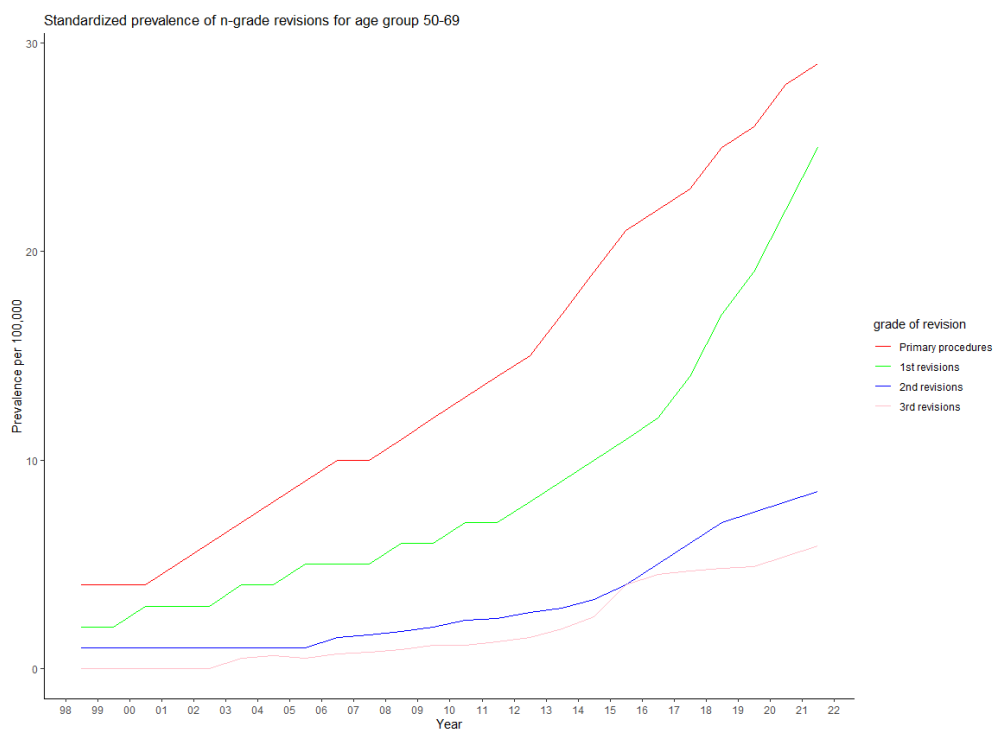Standardized incidence of n-grade revisions for age group 50-69

Only grades of revisions with occurrences >10 are shown; for prevalence, >n grade are reported as well.

Supplementary Figure 10: Standardized annual prevalence (panel A) and incidence rates (panel B) for all n-grade revisions (including major and minor revisions) for <u>age group 70-99.</u>
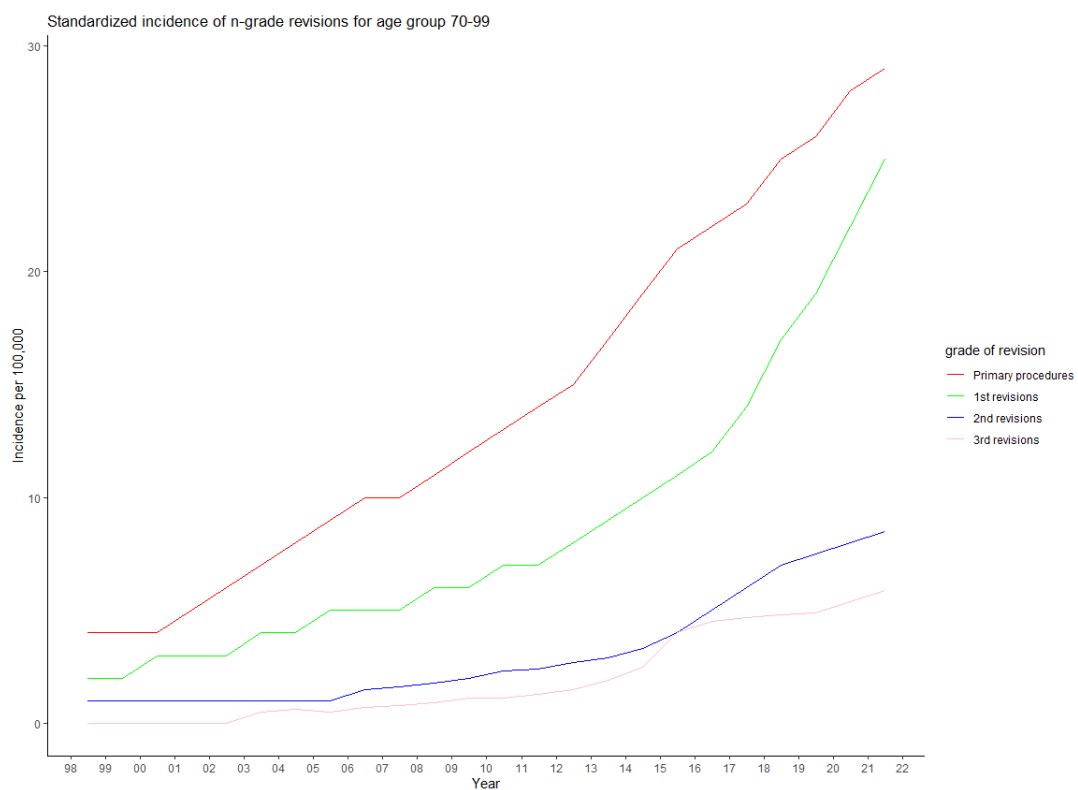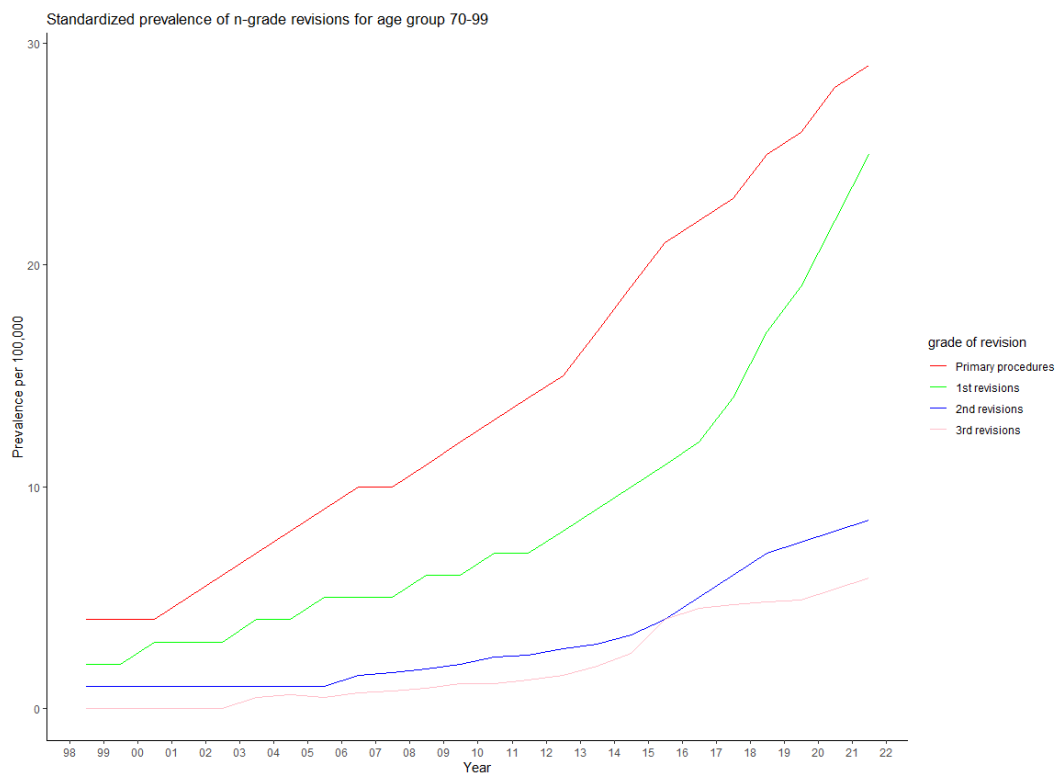
Standardized prevalence of n-grade revisions for age group 70-99

Standardized incidence of n-grade revisions for age group 70-99

Only grades of revisions with occurrences >10 are shown; for prevalence, >n grade are reported as well.

Supplementary table 1: Age-stratified prevalence and incidence of major n-grade revisions for <u>females</u>, Denmark 2021.

Grade of revision	Age group	No. of procedures	No. of persons in Denmark on the 1st of January in 2021	Prevalence per 100.000	Incidence per 100.000
1st	Total				
	18-49				
	50-69				
	70-99				
2nd	Total				
	18-49				
	50-69				
	70-99				
3rd	Total				
	18-49				
	50-69				
	70-99				
4th	Total				
	18-49				
	50-69				
	70-99				
5th	Total				
	18-49				
	50-69				
	70-99				
n-grade	Total				
	18-49				
	50-69				
	70-99				

Only grades of revisions with occurrences >10 are shown.

Supplementary table 2: Age-stratified prevalence and incidence of major n-grade revisions for <u>males</u>, Denmark 2021.

Grade of revision	Age group	No. of procedures	No. of persons in Denmark on the 1st of January in 2021	Prevalence per 100.000	Incidence per 100.000
1st	Total				
	18-49				
	50-69				
	70-99				
2nd	Total				
	18-49				
	50-69				
	70-99				
3rd	Total				
	18-49				
	50-69				
	70-99				
4th	Total				
	18-49				
	50-69				
	70-99				
5th	Total				
	18-49				
	50-69				
	70-99				
n-grade	Total				
	18-49				
	50-69				
	70-99				

Only grades of revisions with occurrences >10 are shown.

Supplementary table 3: Age-stratified prevalence and incidence of all n-grade revisions (including major and minor revisions) for <u>females</u>, Denmark 2021

Grade of revision	Age group	No. of procedures	No. of persons in Denmark on the 1st of January in 2021	Prevalence per 100.000	Incidence per 100.000
1st	Total				
	18-49				
	50-69				
	70-99				
2nd	Total				
	18-49				
	50-69				
	70-99				
3rd	Total				
	18-49				
	50-69				
	70-99				
4th	Total				
	18-49				
	50-69				
	70-99				
5th	Total				
	18-49				
	50-69				
	70-99				
n-grade	Total				
	18-49				
	50-69				
	70-99				

Only grades of revisions with occurrences >10 are shown.

Supplementary table 4: Age-stratified prevalence and incidence of all n-grade revisions (including major and minor revisions) for <u>males</u>, Denmark 2021

Grade of revision	Age group	No. of procedures	No. of persons in Denmark on the 1st of January in 2021	Prevalence per 100.000	Incidence per 100.000
1st	Total				
	18-49				
	50-69				
	70-99				
2nd	Total				
	18-49				
	50-69				
	70-99				
3rd	Total				
	18-49				
	50-69				
	70-99				
4th	Total				
	18-49				
	50-69				
	70-99				
5th	Total				
	18-49				
	50-69				
	70-99				
n-grade	Total				
	18-49				
	50-69				
	70-99				

Only grades of revisions with occurrences >10 are shown.

6. REFERENCES

1.   Price AJ, Alvand A, Troelsen A, Katz JN, Hooper G, Gray A, et al. Knee replacement. Lancet. 2018;392(10158):1672-82.
2.   Klasan A, Magill P, Frampton C, Zhu M, Young SW. Factors predicting repeat revision and outcome after aseptic revision total knee arthroplasty: results from the New Zealand Joint Registry. Knee Surg Sports Traumatol Arthrosc. 2021;29(2):579-85.
3.   Maradit Kremers H, Larson DR, Crowson CS, Kremers WK, Washington RE, Steiner CA, et al. Prevalence of Total Hip and Knee Replacement in the United States. J Bone Joint Surg Am. 2015;97(17):1386-97.
4.   Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. Jama. 2017;318(23):2337-43.
5.   Hiemstra B, Keus F, Wetterslev J, Gluud C, van der Horst ICC. DEBATE-statistical analysis plans for observational studies. BMC Med Res Methodol. 2019;19(1):233.

7. SAP REPORTING GUIDELINE

This SAP has been reported according to the items recommended by the DEBATE guideline for statistical analysis plans for observational studies (4, 5).

Table A. Recommended content of statistical analysis plans for observational studies

Section/Item	Index	Description	Location in this SAP
Section 1: Administrative Information			
Title and trial registration	1a	Descriptive title that matches the protocol, with SAP either as a forerunner or subtitle, and study acronym	*Front page*
	1b	Study registration number	-
SAP version	2	SAP version number with dates	*Front page*
Protocol version	3	Reference to version of protocol being used	*Front page*
SAP revisions	4a	SAP revision history	*Front page*
	4b	Justification for each SAP revision	*Front page*
	4c	Timing of SAP revisions in relation to planned repetitive analyses	-
Roles and responsibility	5	Names, affiliations, and roles of SAP contributors	*Front page*
Signatures of:	6a	Person writing the SAP	*Front page*
	6b	Senior statistician responsible	*Front page*
	6c	Chief investigator/clinical lead	*Front page*
Section 2: Introduction			
Background and rationale	7	Synopsis of study background and rationale including a brief description of research question and brief justification for undertaking the study	*1. Study overview*
Objectives	8	Description of specific objectives and hypotheses, including secondary objectives	*1. Study overview*
Section 3: Study Methods			
Study design	9	Brief description of study design including type of study (e.g. case-control, cross-sectional or cohort study)	*1. Study overview*
Power considerations	10	In case of an unspecified sample size, provide power calculations for (at least) the primary analysis or present a detectable difference with a specified power	*1. Study overview*
Framework	11	Superiority, equivalence, or noninferiority hypothesis testing framework, including which comparisons will be presented on this basis	-
Statistical interim analyses and stopping guidance	12a	Information on repetitive analyses specifying what repetitive analyses will be carried out and listing of time points	*1. Study overview*
	12b	Any planned adjustment of the significance level due to repetitive analyses	*1. Study overview*
	12c	Details of guidelines for stopping the study early	-
Timing of final analysis	13	Timing of final analysis, e.g., all outcomes analysed collectively or timing stratified by planned length of follow-up	*1. Study overview*
Timing of outcome assessments	14	Time points at which the outcomes are measured including visit "windows"	*2. Tabular presentation of timing of outcome measurements*
Section 4: Statistical Principles			
	15	Level of statistical significance	*1. Study overview*

Confidence intervals and *P* values	16	Description and rationale for any adjustment for multiplicity and, if so, detailing how the type 1 error is to be controlled	*1. Study overview*
	17	Confidence intervals to be reported	*1. Study overview*
Adherence and protocol deviations	18a	Definition of protocol deviations for the study	*4. Protocol deviations with bearing on this statistical analysis plan*
	18b	Description of which protocol deviations will be summarized	*4. Protocol deviations with bearing on this statistical analysis plan*
Analysis populations	19	Definition of analysis populations, eg, intention to treat, per protocol, complete case, safety	*5. Outline (for each table and figure)*
Section 5: Study Population			
Screening data	20	Reporting of screening data (if collected) to describe representativeness of trial sample	*5. Outline (Figure 1)*
Eligibility	21	Summary of eligibility criteria	*1. Study overview*
Recruitment	22	Information to be included in the STROBE flow diagram	*5. Outline (Figure 1)*
Withdrawal/follow-up	23a	Level of withdrawal, e.g., dropouts after inclusion or refusal to be contacted for additional information	*5. Outline (Figure 1)*
	23b	Timing of withdrawal/lost to follow-up data	*5. Outline (Figure 1)*
	23c	Reasons and details of how withdrawal/lost to follow-up data will be presented	*5. Outline (Figure 1)*
Baseline patient characteristics	24a	List of baseline characteristics to be summarized	*5. Outline (Table 1)*
	24b	Details of how baseline characteristics will be descriptively summarized	*5. Outline (Table 1)*
Potential confounding covariates	25	A description of potential confounding covariates and how these will be dealt with	-
Section 6: Analysis			
Outcome definitions		List and describe each primary and secondary outcome including details of:	
	26a	Specification of outcomes and timings. If applicable include the order of importance of primary or key secondary endpoints (e.g., order in which they will be tested)	*5. Outline (mainly Table 2)*
	26b	Specific measurement and units (e.g., glucose control, HbA1c [mmol/mol or %])	*5. Outline*
	26c	Any calculation or transformation used to derive the outcome (e.g., change from baseline, QoL score, time to event, logarithm, etc)	*5. Outline, and 3. Elaborations on outcomes and data*
Analysis methods	27a	What analysis method will be used and how the treatment effects will be presented	*5. Outline*
	27b	Any adjustment for covariates	*5. Outline*
	27c	Methods used for assumptions to be checked for statistical methods	*5. Outline*
	27d	Details of alternative methods to be used if distributional assumptions do not hold, eg, normality, proportional hazards, etc	*5. Outline*
	27e	Any planned sensitivity analyses for each outcome where applicable	*5. Outline*
	27f	Any planned subgroup analyses for each outcome including how subgroups are defined	*5. Outline*
Missing data	28	Reporting and assumptions/statistical methods to handle missing data (e.g., multiple imputation)	*5. Outline*
Additional analyses	29	Details of any additional statistical analyses required, eg, complier-average causal effect analysis	*5. Outline*
Harms	30	Only applies when intervention effects are studied. Sufficient detail on summarizing safety data, e.g. information on severity, expectedness, and associations; details of how adverse events are scored; how adverse event data will be analysed and the follow-up time.	*5. Outline*
Statistical software	31	Details of statistical packages to be used to carry out analyses	*1. Study overview*
References	32a	References to be provided for nonstandard statistical methods	*6. References*
	32b	Reference to Data Management Plan	-

32c	Reference to the Study Master File and Statistical Master File	-
32d	Reference to other standard operating procedures or documents to be adhered to	-

Abbreviations: STROBE, STrengthening the Reporting of OBservational studies in Epidemiology; HbA1c, hemoglobin A1c; QoL, quality of life; SAP, statistical analysis plan.