

## **Supplementary material**

Appendix 1. Description of registries and diagnostic tests

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## Appendix 1

### Registries and diagnostic test

Data were extracted from the following registries:

The Danish Civil Registration System, established in 1967, was used to identify the members of the population comparison cohort and siblings and parents (family members) of the LNB patients and members of the population comparison cohort.<sup>1</sup> We also used this registry to extract data on gender, date of birth, immigration/emigration, loss to follow-up, death, and date of birth of children of all study participants.

The Danish National Patient Registry, established in 1977, records data on all patients discharged from non-psychiatric hospitals. Since 1994 it has also included data on all visits to outpatient departments and emergency clinics in Denmark.<sup>1-3</sup> Diagnoses are coded by the attending physician according to the International Classification of Diseases, Eighth Revision [ICD-8] until 31 December 1993 and thereafter by the Tenth Revision [ICD-10].<sup>2</sup> From this registry we extracted clinical diagnoses of Lyme borreliosis, multiple sclerosis, cerebral infarction, heart block, skin diseases, and diagnoses used to calculate Charlson Comorbidity Index scores.<sup>4</sup>

The Danish Cancer Registry was established in 1943. Since March 1987 reporting of data on all malignant diseases has been mandatory. Approximately 90% of cases in the registry are verified by histological examination. An extensive data validation program ensures the quality and completeness of registry data.<sup>5</sup> From this registry, we extracted data on cancer diagnoses.

Statistics Denmark provided access to the following registries:

The Danish Educational Attainment Registry, from which we extracted data on educational achievement of members of the study cohorts in each calendar year. In total, 97% of the ethnic Danish population has non-missing educational information in the registry, with an estimated misclassification rate of 0% to 3%. From this registry, we also obtained data on mathematics grades in primary school.<sup>6</sup>

The Employment Classification Module provided data on the employment status of study participants in each calendar year of the study period. It also provided data on receipt of disability pensions starting on January 1, 1991.<sup>7, 8</sup>

Personal Income Statistics provided data on the personal income of study cohort members in each calendar year during the study period.<sup>7</sup>

### Detection of *B.burgdorferi* intrathecal antibodies

*B.burgdorferi*-specific intrathecal antibody production was measured by using capture enzyme-linked immunosorbent assays (ELISA).<sup>9</sup> The assays used native purified flagella antigen. The assay measures the proportion of specific antibodies to the total immunoglobulin in paired CSF and serum samples. An increased proportion of specific antibodies in CSF directly reflect intrathecal antibody synthesis. The test result was expressed as a specific capture antibody index  $OD\text{-CSF}/OD\text{-serum} \times (OD\text{-CSF} - OD\text{-serum})$ . Definite *B.burgdorferi* intrathecal antibody synthesis was assumed if the specific capture IgG and/or IgM antibody index was  $\geq 0.3$ .

## Appendix 2

### Codes used in the study

Borreliosis: ICD-8: 10499 and ICD-10: A69.2

Multiple sclerosis: ICD-8: 34000 - 34809 and ICD-10: G35.0 - G35.9

Arthritis: ICD-8: 71000 - 71599 and ICD-10: M00.0-M03.9

Skin diseases: ICD-8: 70190 and ICD-10: L90.4, L90.5, L90.8, L90.9

Cerebral infarction: ICD-8: 43000-43899 and ICD-10:I63.0-I66.9

Heart block and cardiac arrest: ICD-8: 42720-42799 and ICD-10 I44.0-I44.6, I45.0-I46.9.

Cancers were coded according ICD-9/ICD-10 during the complete study period.

Cancer excluding non-melanoma skin cancer: C00.0 – C43.9 & C45.0-C99.9

Non-hematologic cancer: C00.0 – C80.9

Hematologic cancer (Lymphoma, Leukemia, Myelomatosis): C81.0-C96.9

Lymphoma C81.0 – C88.9

Myelomatosis C90.0-C90.2

Leukemia (not chronic lymphatic leukaemia) C91.0 & C91.2-C95.9

Chronic lymphatic leukemia C91.1

Non-melanoma skin cancer: C44.0-C44.9

## Appendix 3

### Supplementary figures

Figure A. Study flowchart. LNB: Lyme neuroborreliosis

Figure B. Cumulative survival (A) and cumulative incidence of hematologic cancer (B) (%), in family members of patients with Lyme neuroborreliosis (black line) and family members of the population comparison cohort (grey line).

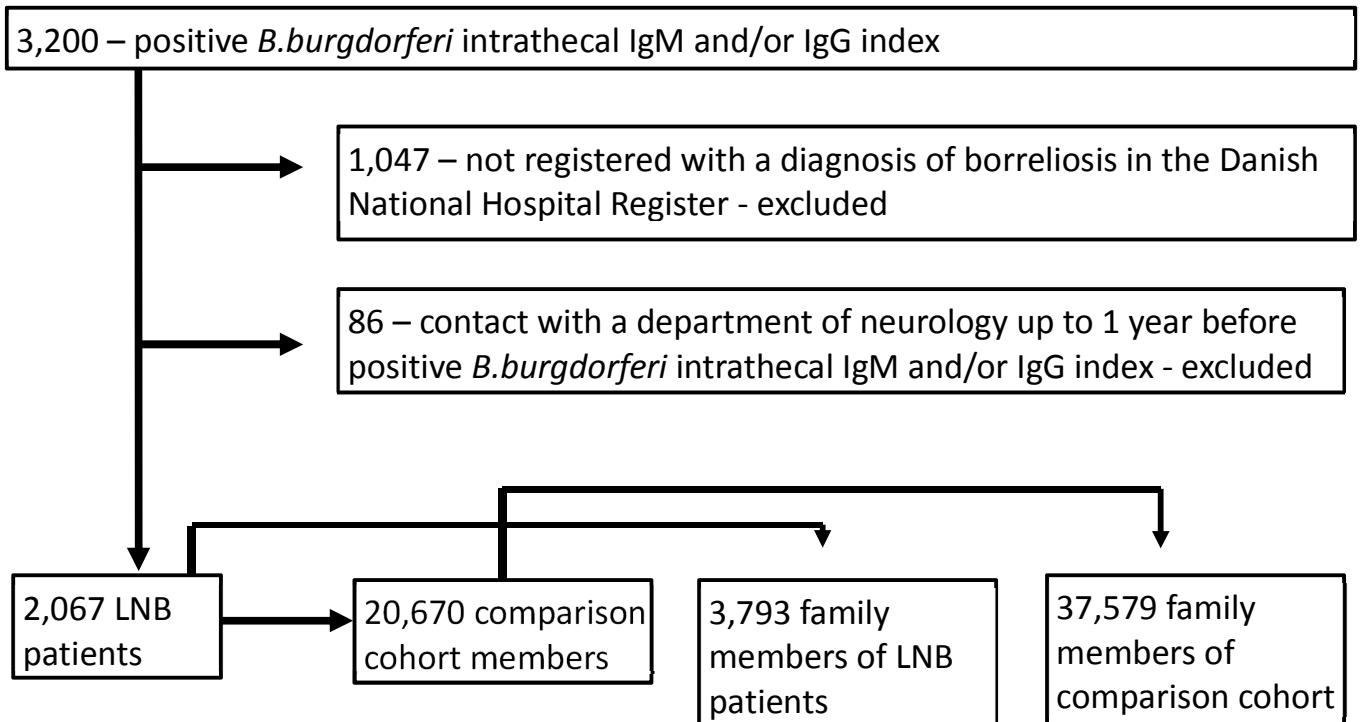
Figure C. Cumulative incidence of multiple sclerosis (%) (A), cumulative survival after diagnosis of hematologic cancer (B), and proportion visiting a department of hematology (C) or neurology (D) (%) for patients with Lyme neuroborreliosis (black) and members of the population comparison cohort (grey).

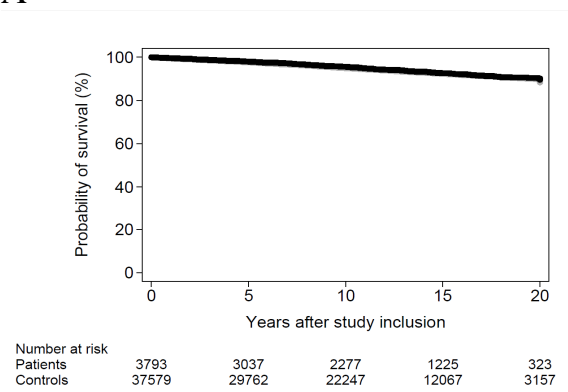
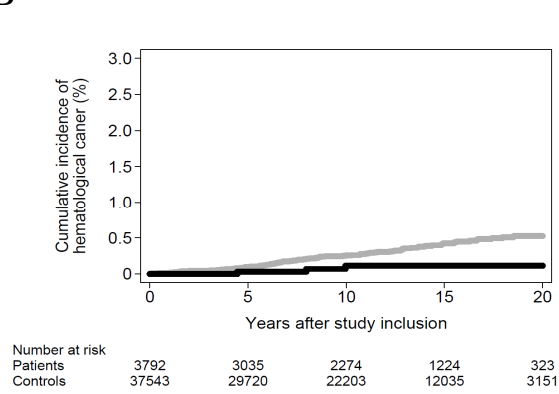
Figure D. Mean number of inpatient hospital days/year, mean number of outpatient hospital visits/year in patients with Lyme neuroborreliosis (black) and members of the population comparison cohort (grey) (left, A and B) and in family members of patients with Lyme neuroborreliosis (black) and family members of the population comparison cohort (grey) (right, C and D).

Figure E. Proportion employed (%), mean income (1000 Danish krone/year) and mean number of sick leave days in patients with Lyme neuroborreliosis (black) and members of the population comparison cohort (grey) (left, A, B and C) and in family members of patients with Lyme neuroborreliosis (black) and family members of the population comparison cohort (grey) (right, D, E and F).

Figure F. Proportion married (%), proportion divorced (%), mean number of children in patients with Lyme neuroborreliosis (black) and members of the population comparison cohort (grey) (left, A, B and C) and in family members of patients with Lyme neuroborreliosis (black) and family members of the population comparison cohort (grey) (right, D, E and F).

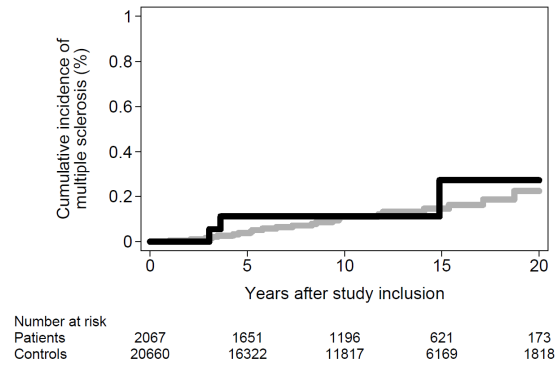
Supplementary Figure A



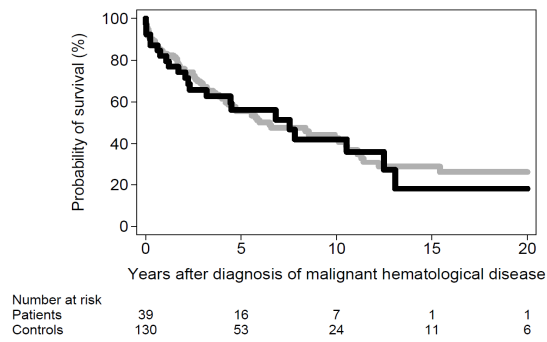
**Supplementary Figure B****A****B**

## Supplementary Figure C

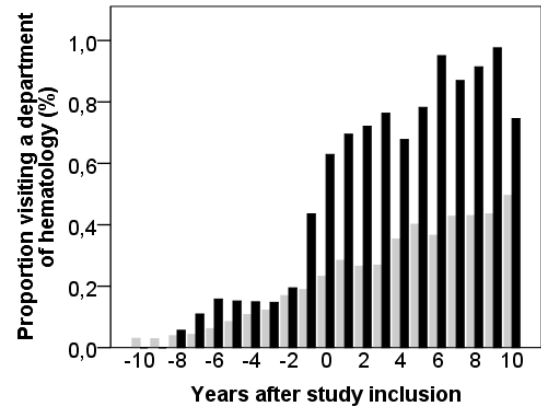
A



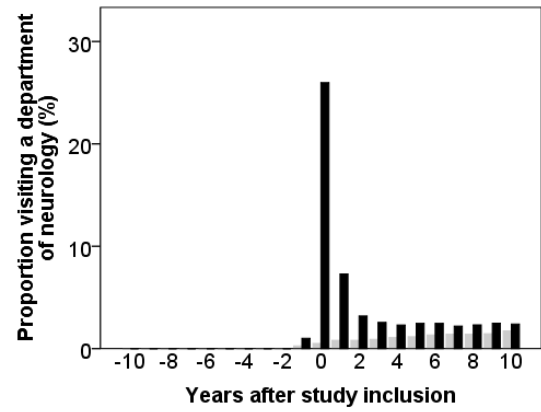
B



C

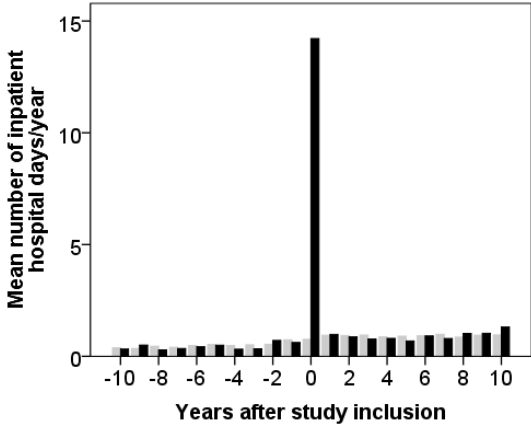


D

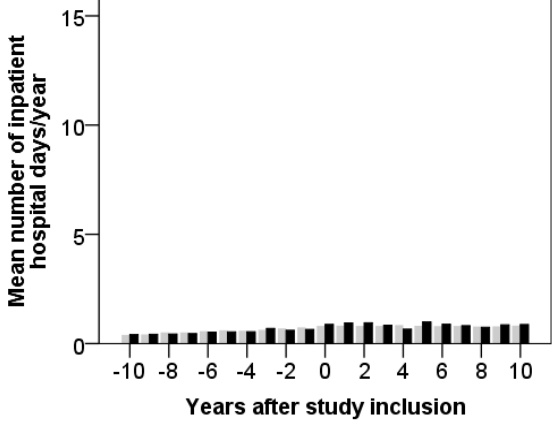


Supplementary Figure D

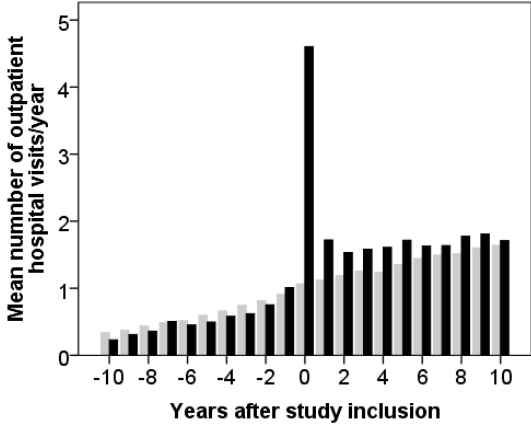
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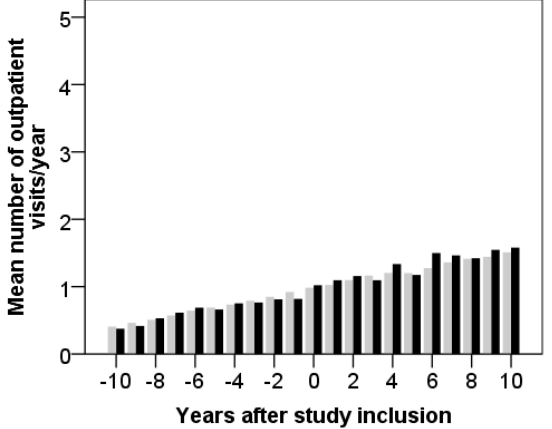
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B

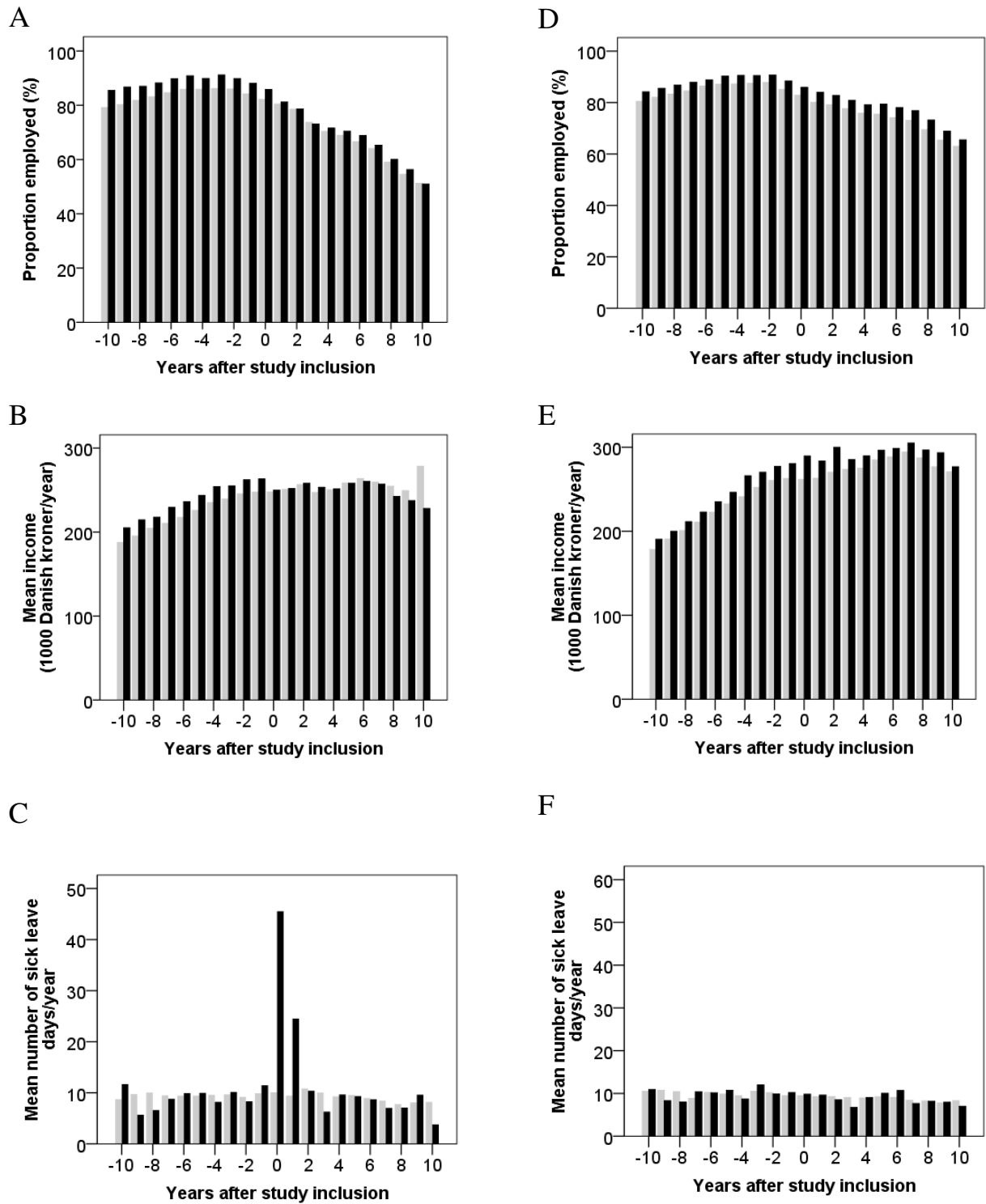


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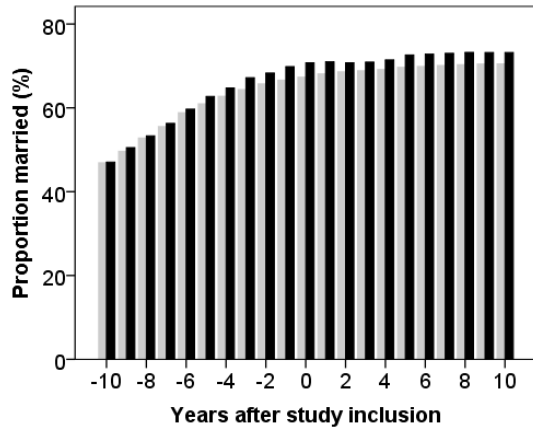


Supplementary Figure E

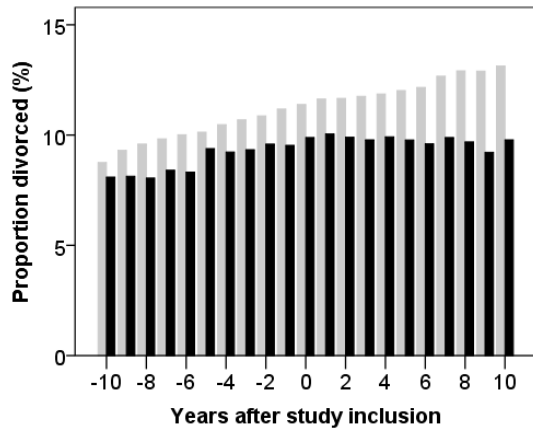


Supplementary Figure F

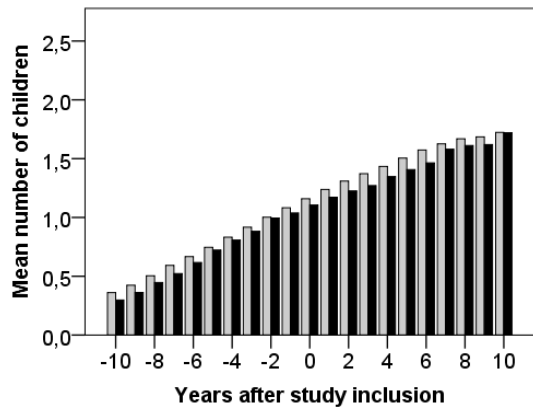
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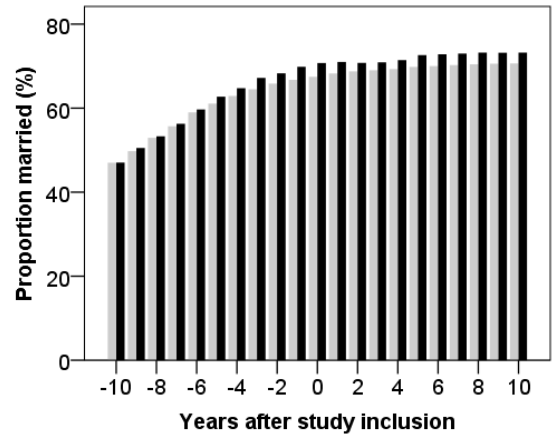
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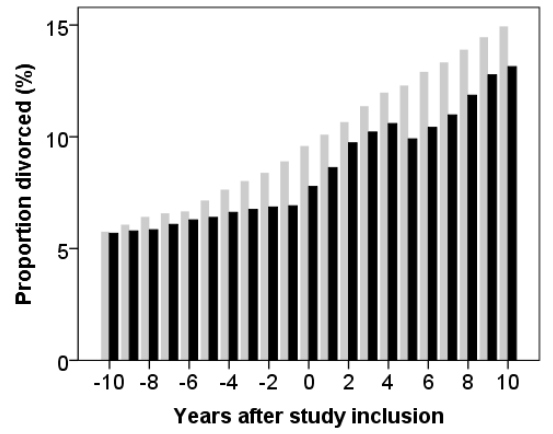
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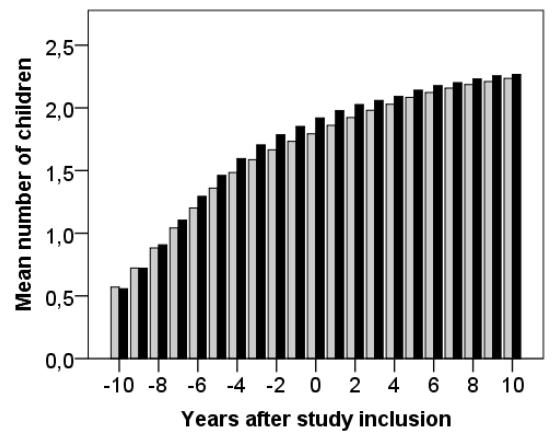
D



E



F



## Appendix 4:

### References

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