ONLINE APPENDIX

Antidepressant Use Before and After the Diagnosis of Type 2 Diabetes: A Longitudinal Modeling Study

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Figure S1. Flow Chart of Diabetes Case-Control Selection

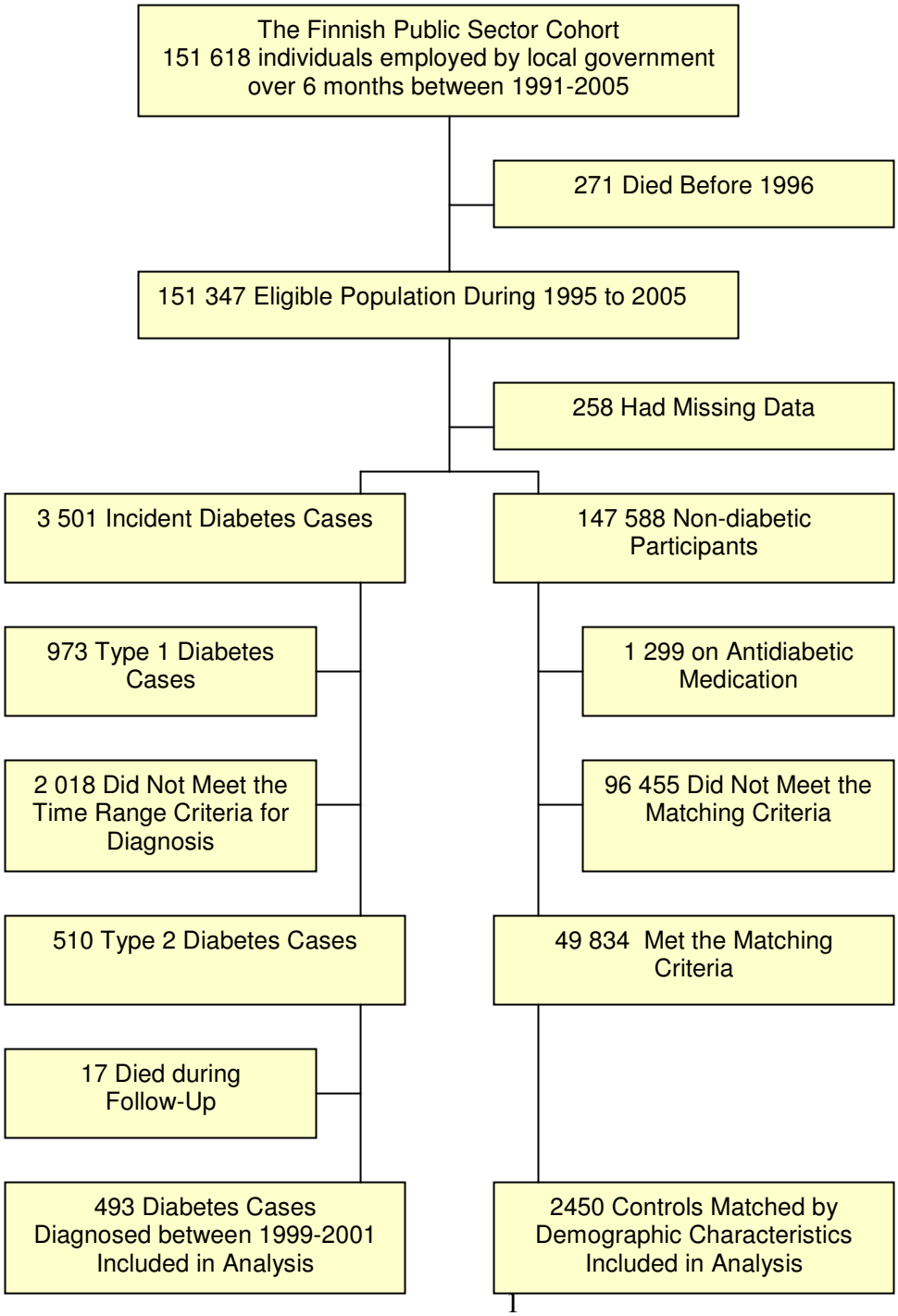
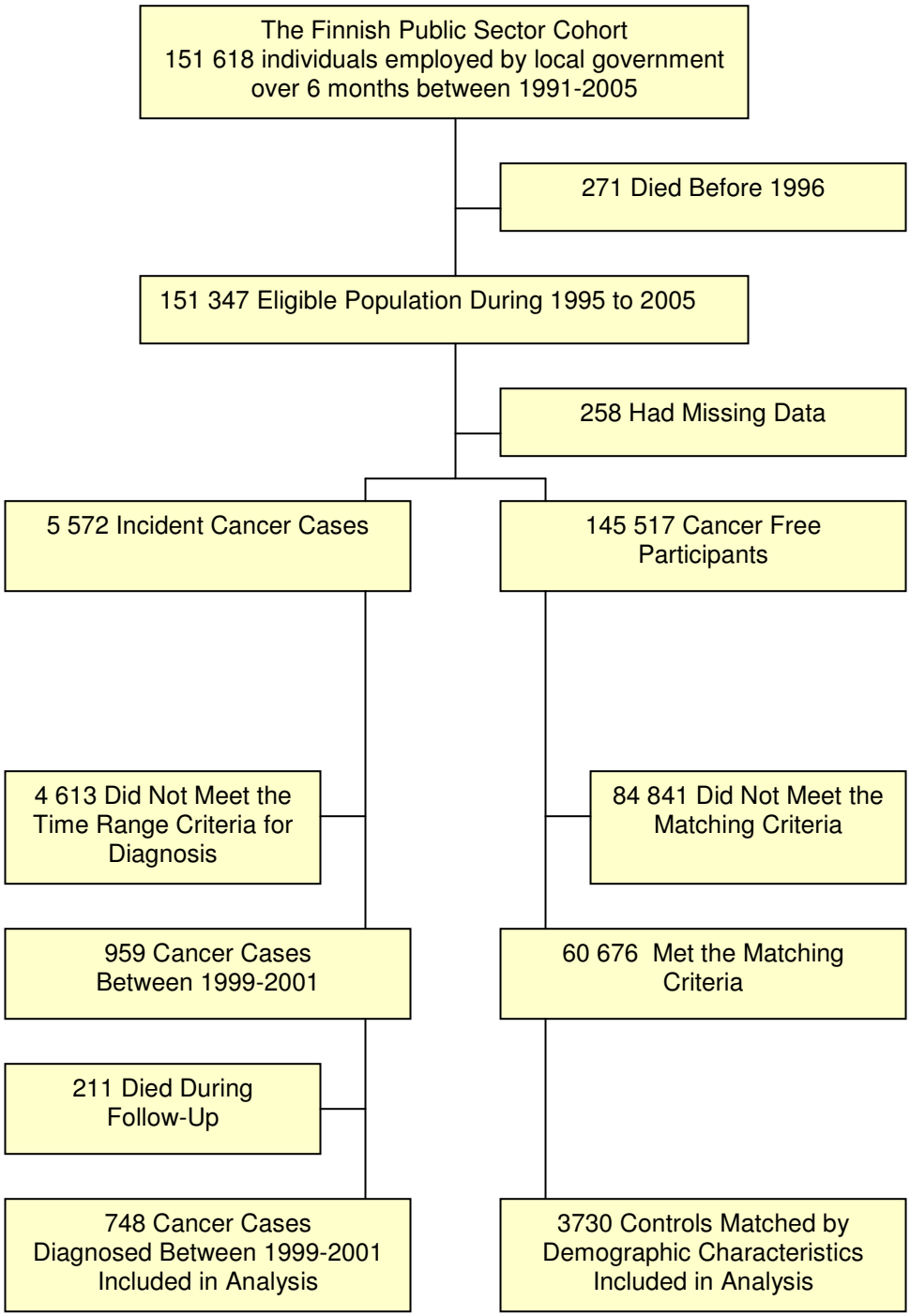


Figure S2. Flow Chart of Cancer Case-Control Selection



Longitudinal Analysis of Antidepressant Use

We applied a repeated-measures logistic regression analysis using the generalized estimating equations (GEE) method to estimate trajectories of antidepressant use before and after the diagnosis. Data were structured so that the repeated measurements were nested within participants (i.e., the same individuals contributed more than one observations to the dataset) and the non-independence of the within person observations was taken into account in estimating the standard errors. Differences in trajectories between incident cases and controls were modeled in multiple steps. We created 3 time variables to describe temporal changes: observation time (a continuous variable ranging from -4 to +4), time at diagnosis (a dummy variable, 1=at year 0 and 0=all other times) and period (a dummy variable, 0=years -4 to 0 and 1=years +1 to +4, to separate periods before and after the diagnosis). We adjusted all models for age, sex, and calendar year of diagnosis. We determined the final model with a backward elimination procedure by first fitting a model with interactions between case status and time variables in addition to their main effects and then removing step-by-step the non-significant interaction terms and main effects. Non-significant main effects were retained when the term for their interaction was significant.

Table S1. Fixed Effects for Repeated Measures Logistic Regression GEE Model of Antidepressant Use Before and After the Diagnoses of Type 2 Diabetes Mellitus and Cancer (Caseness)

	Diabetes study (n = 2943, 26,487 measurements)			Cancer study (n = 4478, 40,302 measurements)		
	Beta	SE	P-value	Beta	SE	P-value
Adjustment						
Sex	0.474	0.118	<0.0001	0.519	0.130	<0.0001
Age	-0.008	0.007	0.21	-0.004	0.005	0.37
Calendar year of diagnosis	0.112	0.069	0.11	0.105	0.054	0.05
Terms for Controls						
Time*	0.083	0.007	<0.0001	0.116	0.017	<0.0001
Diagnosis year†	-0.033	0.067	0.62	—	—	Dropped
Period‡	—	—	Dropped	0.050	0.066	0.45
Time* x Period‡	—	—	Dropped	-0.042	0.026	0.10
Terms for Cases						
Caseness	0.659	0.126	<0.0001	0.300	0.138	0.03
Caseness x Time*	—	—	Dropped	0.049	0.039	0.21
Caseness x Diagnosis year†	0.310	0.123	0.01	—	—	Dropped
Caseness x Period‡	—	—	Dropped	0.403	0.141	0.004
Caseness x Time* x Period‡	—	—	Dropped	-0.143	0.056	0.01

These models are illustrated in Figure 2, Panels A (Diabetes study) and B (Cancer study).

* A continuous variable ranging from -4 to 4 and centered at the time of diagnosis (Time=0).

† A dummy variable to capture the effect of the year of diagnosis. Thus, Diagnosis year = 1 when Time is 0; Diagnosis year = 0 when Time is greater than 0 or Time is smaller than 0.

‡ A dummy variable to capture the effect of post-diagnosis period: Period = 1 when Time is greater than 0; Period = 0 when Time is from -4 to 0.

Sensitivity Analyses

We conducted four sensitivity analyses. First, to examine whether the findings could be driven by false inclusion of type 1 diabetes patients as cases, we repeated the main analysis first excluding all incident cases who were on insulin treatment during the observation period [N=126 (25.6%) at year 4, a total of 9.4% of the observations after the diagnosis] and additionally those aged 35 or less at the time of diagnosis (14 observations among cases)(webtable A1). These exclusions had no effect on the observed antidepressant trajectories.

Second, to examine the role of CHD in the antidepressant trajectories, we repeated the main analysis excluding measurements among subjects with prevalent CHD. This left 25,301 measurements of the total of 26,487 measurements in the analysis (webtable A1). Again, the exclusion did not affect the observed antidepressant trajectories.

Third, we repeated the main analysis including additionally socioeconomic position, job contract and geographical area in the model, in order to control residual confounding in all matching variables (webtable A1). The findings remained essentially unchanged.

Fourth, we repeated analyses with SSRIs as the outcome to examine antidepressant trajectories based on a drug with lower risk of cardiotoxicity than tricyclic antidepressants. Of the 493 diabetes cases, 23 (4.7%) were prescribed SSRIs during the first observation year and 49 (9.9%) during the last observation year. The corresponding figures for the 2450 controls were 60 (2.5%) and 105 (4.3%). Findings of the SSRI trajectories (webtable A2) were largely similar to those presented in Table 2 and Figure 2. The only difference was an absence of a significant temporary increase in SSRI prescription at the year of the diagnosis.

Table S2. Three Sensitivity Analyses: Fixed Effects for the Multilevel Model of Change for Antidepressant Use Before and After the Diagnosis of Type 2 Diabetes (Caseness) in Subcohorts and with Additional Covariates.

	Beta	SE	P-value
Subpopulation excl. those on insulin treatment or younger than 35 (n=2787, 24,678 measurements)			
Sex	0.483	0.121	<0.0001
Age	-0.015	0.008	0.06
Calendar year of diagnosis	0.088	0.071	0.21
Time*	0.076	0.008	<0.0001
Diagnosis year†	-0.052	0.071	0.45
Caseness	0.617	0.131	<0.0001
Caseness x Diagnosis year†	0.328	0.130	0.01
Subgroup excl. those with prevalent CHD (n=2868, 25,301 measurements)			
Sex	0.456	0.121	<0.0001
Age	-0.009	0.007	0.20
Calendar year of diagnosis	0.088	0.071	0.22
Time*	0.082	0.007	<0.0001
Diagnosis year†	-0.066	0.069	0.34
Caseness	0.688	0.129	<0.0001
Caseness x Diagnosis year†	0.379	0.125	0.002
Total cohort with additional covariates (n=2943, 26,487 measurements)			
Sex	0.445	0.126	<0.0001
Age	-0.013	0.007	0.08
Calendar year of diagnosis	0.125	0.070	0.07
SES (vs Higher non-manual)			
Lower non-manual	0.065	0.125	0.70
Manual	0.137	0.161	0.40
Job contract‡	-0.123	0.138	0.37
Geograpical area (vs Area A)			
B	-0.028	0.148	0.85
C	-0.982	0.196	<0.000
D	0.142	0.185	0.44
E	-0.170	0.235	0.47
F	-0.010	0.223	0.96
G	-0.328	0.345	0.34
Diagnosis year†	-0.034	0.069	0.62
Caseness	0.673	0.125	<0.0001
Caseness x Diagnosis year†	0.313	0.125	0.01

* A continuous variable ranging from -4 to 4 and centered at the time of diagnosis (Time=0).
† A dummy variable to capture the effect of the year of diagnosis. Thus, Diagnosis year = 1 when Time is 0; Diagnosis year = 0 when Time is greater than 0 or Time is smaller than 0.
‡ 1=permanent, 2=non-permanent.

Table S3. Sensitivity Analysis with a Specific Antidepressant: Fixed Effects for the Multilevel Model of Change for SSRI Use Before and After the Diagnosis of Type 2 Diabetes (Caseness).

	Beta	SE	P-value
Total cohort with SSRI as the outcome (n=2943, 26487 measurements)			
Sex	0.594	0.140	<0.0001
Age	-0.012	0.008	0.13
Calendar year of diagnosis	0.115	0.081	0.16
Time*	0.082	0.010	<0.0001
Diagnosis year†	0.057	0.067	0.52
Caseness	0.704	0.144	<0.0001
Caseness x Diagnosis year†	0.184	0.160	0.25

* A continuous variable ranging from -4 to 4 and centered at the time of diagnosis (Time=0).
† A dummy variable to capture the effect of the year of diagnosis. Thus, Diagnosis year = 1 when Time is 0; Diagnosis year = 0 when Time is greater than 0 or Time is smaller than 0.
‡ 1=permanent, 2=non-permanent.