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Healthy Longevity

Supplementary appendix

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Supplementary Material

Table of Contents

Supplementary Table 1. Overview of performed sensitivity analyses.	1
Supplementary Table 2. Description of the short-term IPD mortality.	2
Supplementary Table 3. Baseline characteristics in minimally adjusted cohort (used for model 1).	3
Supplementary Table 4. Baseline characteristics in cohort without missing ethnicity data (used for model 4).	6
Supplementary Table 5. Detailed regression results for the models adjusted for IMD & region, underlying health conditions and ethnicity.	8
Supplementary Table 6. Primary analysis with overall and period-specific hazard ratios for the association between IPD and mortality.	10
Supplementary Table 7. Predicted survival times for comparators, cases and cases standardized to the demographics of the control group.	11
Supplementary Table 8. Secondary analyses stratified by vaccination status, age group and underlying comorbidities.	12
Supplementary Table 9. Sensitivity analyses.	14
Supplementary Table 10. Difference in death recording between CPRD GOLD and ONS mortality linkage among comparators eligible for ONS linkage (N = 50,201)	15
Supplementary Figure 1.	16
Supplementary Figure 2.	18

Supplementary Table 1. Overview of performed sensitivity analyses.

Motivation for sensitivity analysis	Analyses performed
Selection Bias due to restricting study population to complete cases	Model 1 before and after excluding individuals with missing IMD and region Model 2 before and after excluding individuals with missing comorbidity information Model 3 before and after excluding individuals with missing ethnicity
Ambiguity of comorbidity coding in GP questionnaire	Model 3 was restricting to comorbidities recorded as “Yes” or “No” instead of interpreting absent responses or “Unknown” as an absence of comorbidity (given there was at least record of “Yes” and “No” in the GP questionnaire)
Misclassification of exposure	Model 3 was restricted to comparators without any primary care record of an IPD infection (see Table 1 for definition)
Matching	To explore the impact of different methods accounting for matching, Model 3 was run with no adjustment for matching, adjustment for the matching variables, and a using a frailty model
Disruption of the COVID-19 pandemic (as a cause of mortality and wider healthcare disruption)	Model 3 was run with follow-up ending on the 31 December 2019
Differences in definitions of CNS disease	Instead of using the definition in Table 1, CNS disease in the non-IPD comparators was restricted to medical records of cerebrospinal fluid leak and ventriculoperitoneal shunt as these were given as examples of CNS disease in the GP questionnaire for the IPD cases

IMD: Index of multiple deprivation. GP: General practice. IPD: invasive pneumococcal disease. CNS: Central nervous system.

Supplementary Table 2. Description of the short-term IPD mortality.

Time of survival	% of individuals (N)
< 30 days	26% (5,275)
30-60 days	3.68% (746)
60-90 days	2.44% (495)
90-120 days	1.81% (368)
> 120 days	44.92% (9,113)
Alive	21.14% (4,288)

A total of 20,285 cases over 65 years of age from the national IPD surveillance programme were included.

Supplementary Table 3. Baseline characteristics in minimally adjusted cohort (used for model 1).

		Cases (N = 13,124)		Comparators (N = 52,019)	
Variable		Median	IQR	Median	IQR
Follow-up in years		3.89	1.45-5.95	1.88	0.85-3.29
Follow-up in days		1420	528-2173	685	310-1203
Variable	Category	N	%	N	%
Age (years)	65-69	2362	18	9368	18.01
	70-74	2723	20.75	10870	20.9
	75-79	2554	19.46	10006	19.24
	80-89	4081	31.1	16258	31.25
	90+	1404	10.7	5517	10.61
Year of infection (reporting date)	2012	1201	9.15	–	–
	2013	1233	9.4	–	–
	2014	1288	9.81	–	–
	2015	1549	11.8	–	–
	2016	1879	14.32	–	–
	2017	1885	14.36	–	–
	2018	2022	15.41	–	–
	2019	2067	15.75	–	–
Gender	Female	52.68	27425	52.72	52.68
	Male	47.32	24594	47.28	47.32
Region	East Midlands	1256	9.57	115	0.22
	East of England	1261	9.61	2635	5.07
	London	1315	10.02	6132	11.79
	North East	661	5.04	458	0.88
	North West	1941	14.79	10550	20.28
	South East	2130	16.23	19131	36.78
	South West	1651	12.58	5257	10.11
	West Midlands	1390	10.59	6877	13.22
	Yorkshire & The Humber	1519	11.57	864	1.66

<i>Ethnicity</i>	<i>Asian</i>	295	2.25	741	1.42
	<i>Black</i>	133	1.01	414	0.8
	<i>Mixed</i>	116	0.88	109	0.21
	<i>Other</i>	65	0.5	240	0.46
	<i>White</i>	8285	63.13	29746	57.18
<i>Index of multiple deprivation in quintiles</i>	<i>1 (least deprived)</i>	2821	21.49	14079	27.07
	<i>2</i>	2536	19.32	11894	22.86
	<i>3</i>	2677	20.4	10634	20.44
	<i>4</i>	2632	20.05	9118	17.53
	<i>5 (most deprived)</i>	2458	18.73	6294	12.1
<i>Asplenia/ Splenectomy</i>	<i>Yes</i>	43	0.33	104	0.2
	<i>Unknown</i>	581	4.43	-	-
	<i>Missing</i>	3563	27.15	-	-
<i>Sickle Cell Disease</i>	<i>Yes</i>	10	0.08	<5	<0.01
	<i>Unknown</i>	558	4.25	-	-
	<i>Missing</i>	3561	27.13	-	-
<i>Coeliac Disease</i>	<i>Yes</i>	44	0.34	213	0.41
	<i>Unknown</i>	588	4.48	-	-
	<i>Missing</i>	3566	27.17	-	-
<i>Malignancy</i>	<i>Yes</i>	2062	15.71	7584	14.58
	<i>Unknown</i>	490	3.73	-	-
	<i>Missing</i>	3557	27.1	-	-
<i>Diabetes</i>	<i>Yes</i>	2201	16.77	8840	16.99
	<i>Unknown</i>	467	3.56	-	-
	<i>Missing</i>	3556	27.1	-	-
<i>Cochlear Implant</i>	<i>Yes</i>	15	0.11	<5	<0.01
	<i>Unknown</i>	618	4.71	-	-
	<i>Missing</i>	3564	27.16	-	-
<i>Chronic respiratory disease</i>	<i>Yes</i>	3456	26.33	9465	18.2
	<i>Unknown</i>	423	3.22	-	-
	<i>Missing</i>	3549	27.04	-	-
<i>Chronic liver disease</i>	<i>Yes</i>	272	2.07	225	0.43
	<i>Unknown</i>	604	4.6	-	-
	<i>Missing</i>	3563	27.15	-	-
<i>Chronic kidney disease</i>	<i>Yes</i>	2123	16.18	12036	23.14
	<i>Unknown</i>	490	3.73	-	-
	<i>Missing</i>	3556	27.1	-	-

<i>Chronic cardiovascular disease</i>	<i>Yes</i>	3178	24.22	9867	18.97
	<i>Unknown</i>	470	3.58	-	-
	<i>Missing</i>	3562	27.14	-	-
<i>CNS disease</i>	<i>Yes</i>	262	2	8275	15.91
	<i>Unknown</i>	608	4.63	-	-
	<i>Missing</i>	3564	27.16	-	-
<i>Immunosuppression</i>	<i>Yes</i>	926	7.06	1213	2.33
	<i>Unknown</i>	661	5.04	-	-
	<i>Missing</i>	3577	27.26	-	-
<i>Influenza vaccine last year</i>	<i>Yes</i>	6288	47.91	37550	72.19
	<i>Missing</i>	5212	39.71	-	-
<i>PPV23 vaccine ever</i>	<i>Yes</i>	6669	50.82	39203	75.36
	<i>Unknown</i>	84	0.64	-	-
	<i>Missing</i>	3521	26.83	-	-

CNS: Central nervous system. PPV23: 23-valent pneumococcal polysaccharide vaccine. Cell counts with less than 5 were suppressed for anonymity.

Supplementary Table 4. Baseline characteristics in cohort without missing ethnicity data (used for model 4).

		Cases (N = 8,336)		Comparators (N =20,875)	
Variable		Median	IQR	Median	IQR
<i>Follow-up in years</i>		4.13	1.72-6.03	1.92	0.87-3.35
<i>Follow-up in days</i>		1509	627.75-2202.25	701	316-1223
Variable	Category	N	%	N	%
<i>Age (years)</i>	<i>65-69</i>	1516	18.19	3901	18.69
	<i>70-74</i>	1781	21.37	4717	22.6
	<i>75-79</i>	1641	19.69	4155	19.9
	<i>80-89</i>	2549	30.58	6163	29.52
	<i>90+</i>	849	10.18	1939	9.29
<i>Year of infection (reporting date)</i>	<i>2012</i>	416	4.99	–	–
	<i>2013</i>	589	7.07	–	–
	<i>2014</i>	835	10.02	–	–
	<i>2015</i>	1052	12.62	–	–
	<i>2016</i>	1368	16.41	–	–
	<i>2017</i>	1338	16.05	–	–
	<i>2018</i>	1484	17.8	–	–
	<i>2019</i>	1254	15.04	–	–
<i>Gender</i>	<i>Female</i>	4491	53.87	11246	53.87
	<i>Male</i>	3845	46.13	9629	46.13
<i>Region</i>	<i>East Midlands</i>	830	9.96	27	0.13
	<i>East of England</i>	768	9.21	709	3.4
	<i>London</i>	729	8.75	3234	15.49
	<i>North East</i>	431	5.17	135	0.65
	<i>North West</i>	1230	14.76	4571	21.9
	<i>South East</i>	1326	15.91	7081	33.92
	<i>South West</i>	1109	13.3	1910	9.15
	<i>West Midlands</i>	877	10.52	2750	13.17

	<i>Yorkshire & The Humber</i>	1036	12.43	458	2.19
<i>Ethnicity</i>	<i>Asian</i>	271	3.25	492	2.36
	<i>Black</i>	123	1.48	276	1.32
	<i>Mixed</i>	102	1.22	77	0.37
	<i>Other</i>	59	0.71	162	0.78
	<i>White</i>	7781	93.34	19868	95.18
<i>Index of multiple deprivation in quintiles</i>	<i>1 (least deprived)</i>	1789	21.46	5372	25.73
	<i>2</i>	1605	19.25	4827	23.12
	<i>3</i>	1683	20.19	4188	20.06
	<i>4</i>	1679	20.14	3996	19.14
	<i>5 (most deprived)</i>	1580	18.95	2492	11.94
<i>Asplenia/ Splenectomy</i>	<i>Yes</i>	38	0.46	45	0.22
<i>Sickle Cell Disease</i>	<i>Yes</i>	8	0.1	<5	<0.01
<i>Coeliac Disease</i>	<i>Yes</i>	33	0.4	92	0.44
<i>Malignancy</i>	<i>Yes</i>	1806	21.67	3129	14.99
<i>Diabetes</i>	<i>Yes</i>	1973	23.67	3688	17.67
<i>Cochlear Implant</i>	<i>Yes</i>	13	0.16	<5	<0.01
<i>Chronic respiratory disease</i>	<i>Yes</i>	3104	37.24	4000	19.16
<i>Chronic liver disease</i>	<i>Yes</i>	247	2.96	104	0.5
<i>Chronic kidney disease</i>	<i>Yes</i>	1897	22.76	4765	22.83
<i>Chronic cardiovascular disease</i>	<i>Yes</i>	2817	33.79	3949	18.92
<i>CNS disease</i>	<i>Yes</i>	235	2.82	3317	15.89
<i>Immunosuppression</i>	<i>Yes</i>	829	9.94	491	2.35
<i>Influenza vaccine last year</i>	<i>Yes</i>	5522	66.24	15543	74.46
<i>PPV23 vaccine ever</i>	<i>Yes</i>	5871	70.43	16331	78.23

CNS: Central nervous system. PPV23: 23-valent pneumococcal polysaccharide vaccine. Cell counts with less than 5 were suppressed for anonymity.

Supplementary Table 5. Detailed regression results for the models adjusted for IMD & region, underlying health conditions and ethnicity.

	Model 1 (only adjusted for matching variables)	Model 2 (adj. for region and IMD)	Model 3 (adj. for region, IMD and underlying health conditions)	Model 4 (adj. for region, IMD, underlying health conditions and ethnicity)
<i>Covariate</i>	<i>HR (95% CI)</i>	<i>HR (95% CI)</i>	<i>HR (95% CI)</i>	<i>HR (95% CI)</i>
Comparator (Ref.)	1	1	1	1
IPD case	4.11 (3.96-4.27)	4.14 (3.95-4.35)	3.74 (3.50-3.99)	3.84 (3.52-4.18)
<i>Region</i>				
East Midlands (Ref.)	-	1	1	1
East of England	-	0.93 (0.79-1.10)	1.00 (0.82-1.23)	1.13 (0.86-1.48)
London	-	0.93 (0.79-1.08)	0.97 (0.80-1.18)	1.21 (0.95-1.55)
North East	-	1.19 (0.96-1.47)	1.17 (0.89-1.52)	1.41 (1.00-1.99)
North West	-	1.06 (0.91-1.22)	1.01 (0.85-1.21)	1.02 (0.81-1.28)
South East	-	1.00 (0.87-1.16)	1.04 (0.87-1.24)	1.19 (0.95-1.50)
South West	-	1.08 (0.93-1.26)	1.12 (0.93-1.36)	1.33 (1.04-1.70)
West Midlands	-	1.10 (0.95-1.28)	1.11 (0.92-1.34)	1.29 (1.01-1.64)
Yorkshire and the Humber	-	1.17 (0.99-1.38)	1.18 (0.96-1.45)	1.39 (1.08-1.81)
<i>Index of multiple deprivation</i>				
1 – most deprived (Ref.)	-	1	1	1
2	-	0.97 (0.90-1.04)	1.03 (0.94-1.13)	0.97 (0.85-1.10)
3	-	1.06 (0.99-1.15)	1.10 (1.00-1.20)	1.08 (0.95-1.23)
4	-	0.92 (0.85-0.99)	0.92 (0.84-1.02)	0.88 (0.77-1.00)

5 – least deprived	-	1.09 (1.00-1.18)	1.10 (1.00-1.22)	1.17 (1.02-1.35)
<i>Underlying health condition (condition not present as reference)</i>				
Chronic heart condition	-	-	1.25 (1.17-1.34)	1.20 (1.09-1.32)
Chronic lung condition	-	-	1.57 (1.47-1.69)	1.49 (1.36-1.63)
Chronic liver disease	-	-	2.31 (1.72-3.10)	3.27 (2.19-4.87)
Chronic kidney disease	-	-	1.17 (1.09-1.25)	1.13 (1.03-1.24)
Asplenia/spleen dysfunction	-	-	1.07 (0.56-2.04)	0.75 (0.31-1.81)
Sickle cell disease	-	-	0.85 (0.17-4.20)	0.73 (0.08-6.72)
Immunosuppression	-	-	1.27 (1.11-1.46)	1.24 (1.03-1.49)
Malignancy	-	-	1.85 (1.71-2.00)	1.86 (1.67-2.07)
Disease of the CNS	-	-	2.27 (2.09-2.47)	2.3 (2.05-2.59)
Cochlear implant	-	-	0.21 (0.06-0.77)	0.35 (0.05-2.58)
Diabetes	-	-	1.33 (1.23-1.44)	1.29 (1.16-1.43)
Coeliac disease	-	-	0.96 (0.57-1.62)	0.77 (0.38-1.57)
<i>Ethnicity</i>				
South Asian	-	-	-	1
Black	-	-	-	0.81 (0.51-1.29)
Mixed	-	-	-	0.9 (0.51-1.61)
Other	-	-	-	1.39 (0.79-2.47)
White	-	-	-	1.12 (0.86-1.45)

CNS: Central nervous system. Ref.: Reference. CI: confidence interval; HR: hazard ratio; IPD: invasive pneumococcal disease. IMD: Index of Multiple Deprivation.

Supplementary Table 6. Primary analysis with overall and period-specific hazard ratios for the association between IPD and mortality.

Model	Follow-up period	N	N events	HR (95% CI)
Baseline (Model 1)	0-1 year	80,406	5,199	4.47 (4.22-4.73)
	0-2 years	80,406	8,720	4.28 (4.09-4.48)
	0-5 years	80,406	14,240	4.13 (3.97-4.29)
	Overall	80,406	16,315	4.11 (3.95-4.27)
Plus adjustment for IMD and region (Model 2)	0-1 year	65,143	4,592	4.47 (4.16-4.80)
	0-2 years	65,143	7,709	4.30 (4.06-4.56)
	0-5 years	65,143	12,749	4.14 (3.94-4.35)
	Overall	65,143	14,741	4.14 (3.95-4.35)
Plus adjustment for comorbidities (Model 3)	0-1 year	46,696	3,075	4.06 (3.67-4.49)
	0-2 years	46,696	5,162	3.91 (3.61-4.24)
	0-5 years	46,696	8,803	3.73 (3.49-4.00)
	Overall	46,696	10,252	3.74 (3.50-3.99)
Plus adjustment for ethnicity (Model 4)	0-1 year	29,211	2,184	4.28 (3.75-4.90)
	0-2 years	29,211	3,706	3.98 (3.59-4.42)
	0-5 years	29,211	6,559	3.86 (3.53-4.21)
	Overall	29,211	7,772	3.84 (3.52-4.18)

CI: confidence interval; HR: hazard ratio; IPD: invasive pneumococcal disease.

Supplementary Table 7. Predicted survival times for comparators, cases and cases standardized to the demographics of the control group.

Cohort	Group	Median of the predicted restricted mean survival time (IQR)
65-69	Comparators	11.22 (10.81-11.35)
	Cases	8.00 (6.50-9.23)
	std. Cases	9.23 (8.03-9.65)
70-74	Comparators	10.67 (10.18-10.91)
	Cases	6.97 (5.7-8.01)
	std. Cases	8.07 (6.96-8.70)
75-79	Comparators	9.86 (9.04-10.23)
	Cases	5.42 (4.36-6.42)
	std. Cases	6.20 (4.88-6.92)
80-89	Comparators	8.00 (6.86-8.68)
	Cases	3.93 (3.22-4.64)
	std. Cases	4.13 (3.06-4.93)
90+	Comparators	5.68 (4.51-6.41)
	Cases	2.56 (2.14-3.02)
	std. Cases	2.38 (1.73-2.89)
Overall	Comparators	10.75 (9.46-11.95)
	Cases	7.27 (5.69-11.95)
	std. Cases	9.05 (6.37-11.95)

Survival was predicted using the Aalen-Johnson estimator based on models adjusting for region, index of multiple deprivation, and underlying comorbidities (model 3). For cases, we obtained estimates based on the covariate distribution of the IPD cases and a standardized cohort with the same covariate distributions as the comparator population. CI: confidence interval; IQR: interquartile range.

Supplementary Table 8. Secondary analyses stratified by vaccination status, age group and underlying comorbidities.

Subgroup	Stratified by	N	N events	HR (95% CI)
Vaccination status	PPV23 ever	26,422	6,988	3.33 (3.14-3.54)
	No PPV23	5,044	1,210	4.55 (3.8-5.44)
	Inf. last year	23,893	6,386	3.11 (2.92-3.31)
	No Inf. last year	3,546	1,049	4.73 (3.88-5.76)
Age group	65–79 years	8,561	996	4.29 (3.6-5.10)
	70–74 years	9,872	1,450	3.75 (3.27-4.29)
	75–79 years	9,056	1,835	3.95 (3.52-4.45)
	80–89 years	14,360	4,102	3.41 (3.16-3.68)
	90+ years	4,847	1,869	3.00 (2.68-3.34)
Comorbidity	No comorbidity	4,523	818	5.16 (4.17-6.39)
	Diabetes	2,768	1,056	3.21 (2.74-3.77)
	Cardiovascular Disease	4,371	1,953	3.07 (2.74-3.43)
	Respiratory Disease	4,418	1,790	2.76 (2.44-3.12)
	CNS Disease	316	144	2.28 (1.47-3.55)
	Chronic Kidney Disease	3,820	1,678	2.78 (2.47-3.13)
	Malignancy	2,176	923	3.99 (3.34-4.76)
Clinical presentation of IPD	Meningitis	1,818	236	2.16 (1.57-2.97)
	Pericarditis	110	17	1.83 (0.5-6.74)
	Peritonitis	120	21	8.97 (3.07-26.23)
	Pneumonia	32,349	7,252	3.59 (3.4-3.79)
	Arthritis	1,098	191	2.04 (1.43-2.92)
	Sepsis	2,690	525	4.55 (3.71-5.58)
	Bacteraemia	3,232	706	3.99 (3.36-4.74)

IPD-associated HRs were obtained from models adjusting for region, index of multiple deprivation, and underlying comorbidities (model 3). CI: confidence interval; CNS: central nervous system; HR: hazard ratio.

Supplementary Table 9. Sensitivity analyses.

Type of sensitivity analysis	Cohort	Model	N	N events	HR (95% CI)
Selection bias after restricting to no missing region and IMD	Full cohort	Model 1 (baseline)	80406	16315	4.11 (3.95-4.27)
	Cohort with complete data on region and IMD	Model 1 (baseline)	65143	14741	4.2 (4.03-4.38)
Selection bias after restricting to cases with valid comorbidity recording	Cohort with complete data on region and IMD	Model 2 (IMD and region)	65143	14741	4.14 (3.95-4.35)
	Cohort with valid comorbidity recording (primary analysis cohort)	Model 2 (IMD and region)	46696	10252	3.67 (3.46-3.89)
Selection bias after restricting to individuals with no missing ethnicity data	Cohort with valid comorbidity recording (primary analysis cohort)	Model 3 (comorbidities)	46696	10252	3.74 (3.5-3.99)
	Cohort with complete ethnicity data	Model 3 (comorbidities)	29211	7772	3.82 (3.5-4.16)
Removing IPD cases in comparator population	Primary analysis cohort	Model 3 (comorbidities)	46696	10252	3.74 (3.5-3.99)
	IPD exclusion in comparators	Model 3 (comorbidities)	46531	10221	3.76 (3.52-4.02)
Including or excluding unknown values in GP questionnaire	Primary analysis cohort	Model 3 (comorbidities)	46696	10252	3.74 (3.50-3.99)
	Cohort with complete recording of comorbidities in IPD cases	Model 3 (comorbidities)	41822	9234	3.70 (3.45-3.97)
Limiting follow-up to 31 December 2019	Primary analysis cohort	Model 3 (comorbidities)	46696	10252	3.74 (3.50-3.99)
	Primary analysis cohort restricting follow-up to 31 December 2019	Model 3 (comorbidities)	46696	6147	3.74 (3.46-4.04)
Different methods to adjust for the matching	Primary analysis cohort	Model 3 stratified by matching	46696	10252	3.74 (3.5-3.99)
	Primary analysis cohort	Model 3 with no adjustment for matching	46696	10252	3.44 (3.28-3.61)
	Primary analysis cohort	Model 3 with adjustment for	46696	10252	3.55 (3.38-3.72)

		matching variables			
	Primary analysis cohort	Model 3 with frailty term based on matching ID	46696	10252	3.66 (3.48-3.84)

CI: confidence interval; HR: hazard ratio; IMD: index of multiple deprivation; IPD: invasive pneumococcal disease.

Supplementary Table 10. Difference in death recording between CPRD GOLD and ONS mortality linkage among comparators eligible for ONS linkage (N = 50,201)

<i>Overall number of deaths recorded by dataset</i>	
Number of deaths recorded in CPRD	5,779
Number of deaths recorded in ONS prior to censoring	5,207
Number of deaths recorded in either CPRD or ONS	5,5995
Number of deaths recorded in both CPRD and ONS	4,991
Number of deaths recorded in ONS only	215
Number of deaths recorded in CPRD only	641
<i>Differences in date recording of death date where recorded in both CPRD and ONS</i>	
Number (%) of deaths recorded on the same day between both datasets for individuals eligible for ONS linkage	3,839 (74.70%)
Median number (IQR) difference in days between ONS mortality linkage death date and CPRD death date in individuals eligible for ONS linkage	0 (0-1)
Number (%) of individuals with more than a week difference of recorded death date between ONS mortality linkage and CRPD	576 (9.61%)

CPRD: Clinical Practice Research Datalink. ONS: Office for National Statistics. IQR: Interquartile range.

¹The number of deaths recorded in either of the datasets (N = 7,417) was used as denominator. ²The number of deaths in individuals eligible for linkage was used as a denominator (N= 5,995).

Supplementary Figure 1.

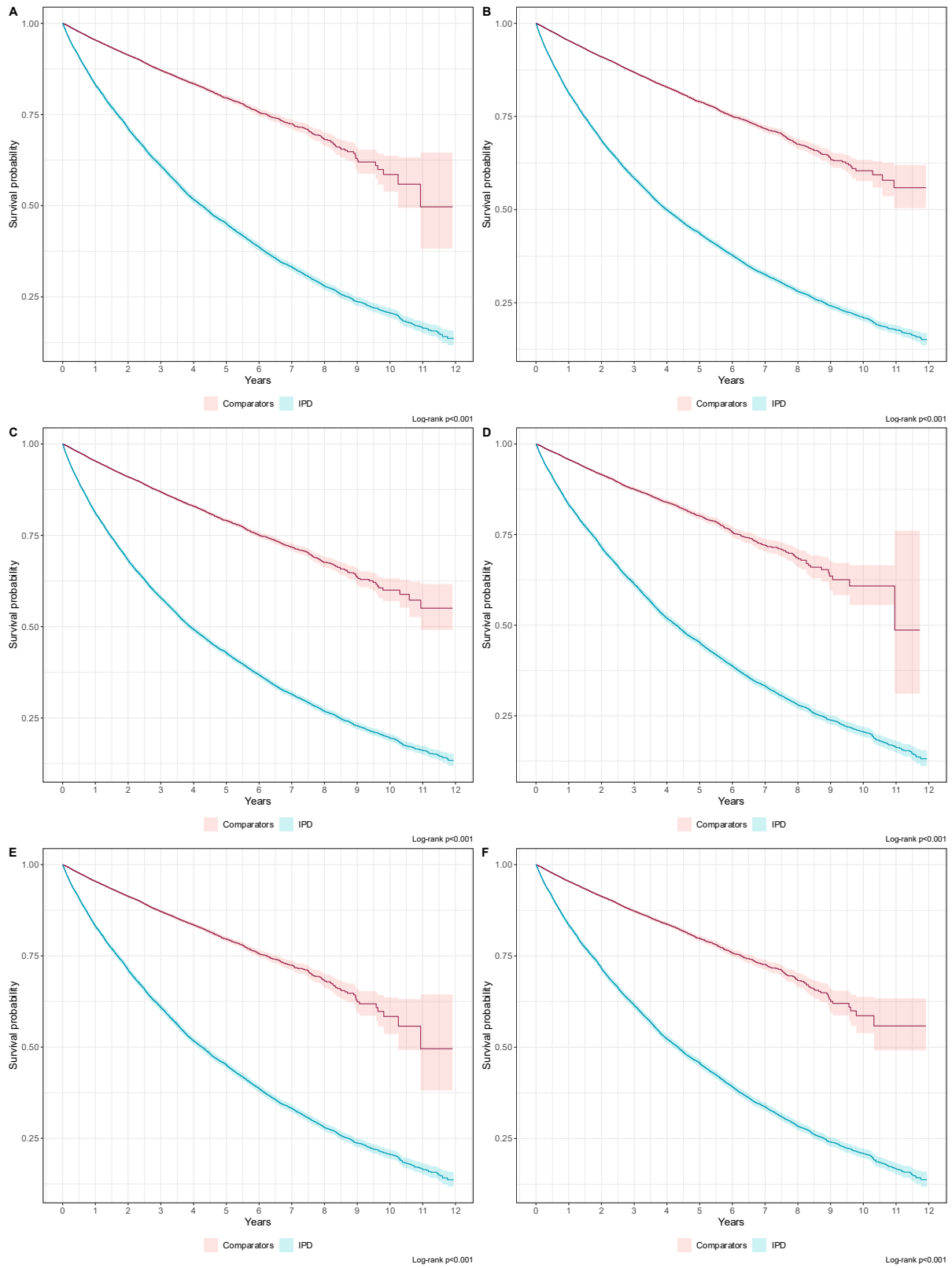


Figure S1. Kaplan-Meier curve comparing the survival of individuals with IPD and non-IPD comparators matched by age, gender, and calendar date. For IPD cases, Day 0 (index date) corresponds 120 days after the recorded date of infection. Kaplan-Meier steps were delayed until 5 events had occurred as a precaution against small number disclosures. A) compares the survival for the main study cohort (individuals with missing deprivation, region and comorbidity data removed), B) the baseline cohort C) the cohorts after removing missing region and deprivation data, and D) the cohort after missing removing missing ethnicity, E) the cohort after removing IPD records in CPRD (sensitivity analysis), and F) the cohort with the more conservative approach of defining comorbidities in the GP questionnaire (sensitivity analysis).

Supplementary Figure 2.

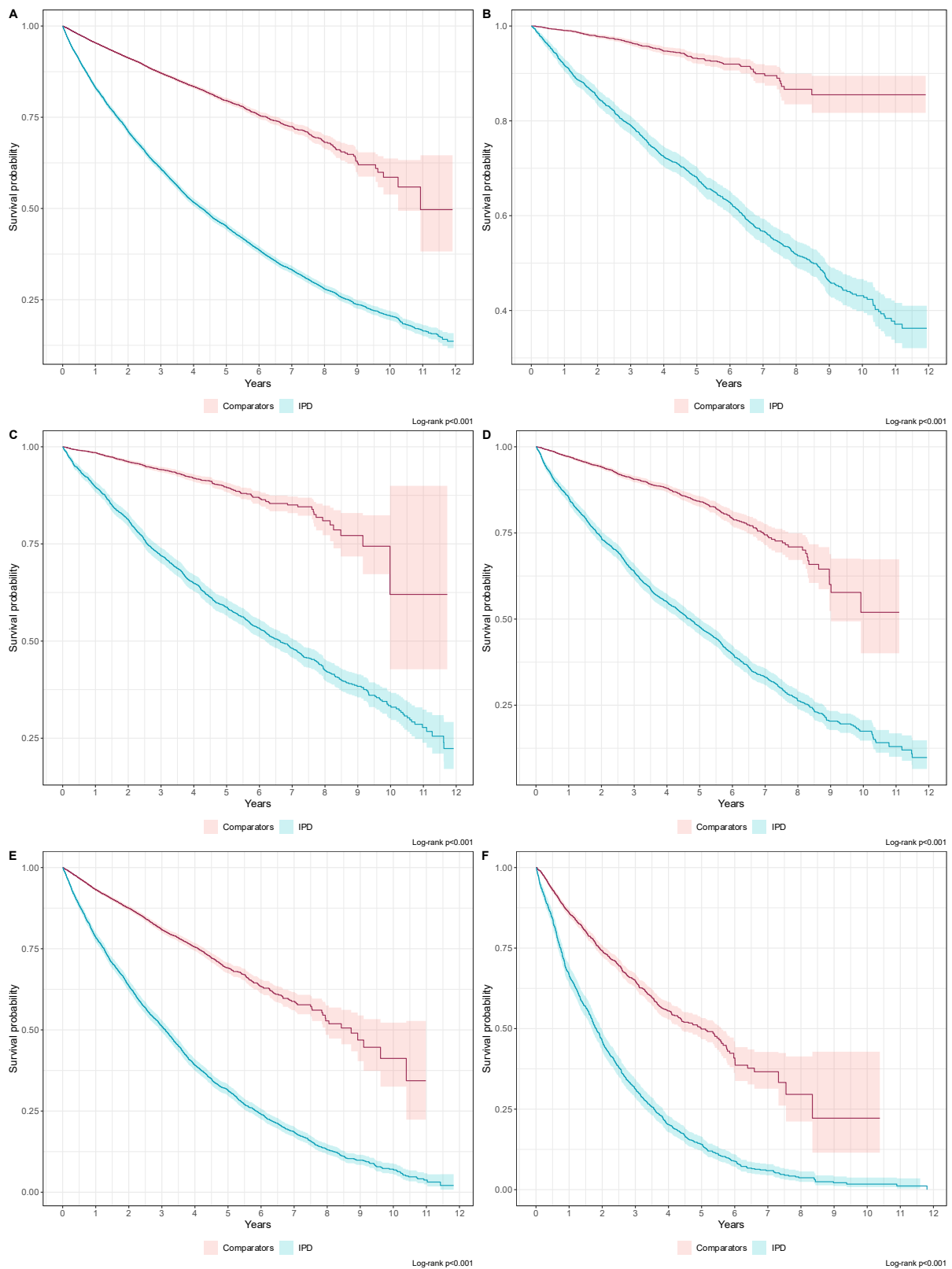


Figure S2. Kaplan-Meier curve comparing the survival of individuals with IPD and non-IPD comparators matched by age, gender, and calendar date. For IPD cases, Day 0 (index date) corresponds 120 days after the recorded date of infection. Kaplan-Meier steps were delayed until 5 events had occurred as a precaution against small number disclosures. A) shows the main study cohort, B) individuals between 65-

69 years, C) individuals between 70-74 years, D) individuals between 75-79 years, E) individuals between 80-89 years and F) Over 90 years old for the main cohort.