Study Report

1. Title Page

Title	TARGET-EU: Comparison of single-device vilanterol/fluticasone furoate with other single-device inhaled corticosteroid and long-acting beta agonist combinations in the risk of pneumonia in adolescents with asthma
Aim	The primary objective is to assess whether vilanterol/fluticasone furoate increases the risk of pneumonia compared to other fixed dose combinations of an inhaled corticosteroid and long-acting beta-2 adrenoceptor agonist (ICS+LABA) in a single-device in adolescent asthma patients
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Study registration	**Site:** https://catalogues.ema.europa.eu/node/4893/administrative-details **Identifier:** EUPAS1000000989 *This study is part of the TARGET EU study with registration details:* **Site:** https://catalogues.ema.europa.eu/node/4440/administrative-details **Identifier:** EUPAS1000000539
Sponsor	**Organization:** EU PE&PV research network **Contact:** eupepv@uu.nl
Conflict of interest	None
Disclaimer and acknowledgement	This document has been produced by making use of the results under the specific contract no.04 FWC EMA/2020/46/TDA/ L5.06 between EU PE&PV Research Network (coordinated by Utrecht University), and the European Medicines Agency. This document expresses the opinion of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties. This study has been registered in the HMA-EMA Catalogue of Real-World Data under the EU PAS numbers: EUPAS1000000539, EUPAS1000000989
Abstract	**Objectives:** The main objective of this non-interventional cohort study was to assess whether vilanterol+fluticasone (V+FF) increases the risk of pneumonia compared to other inhaled corticosteroid + single-device long-acting beta-2 adrenoceptor agonist combinations (ICS+LABA) in adolescent patients with asthma already treated with ICS. **Methods:** We developed a target trial protocol including estimands and key design and analysis elements, based on the estimand framework and emulated this target trial in a non-interventional study. The risk of pneumonia between initiators of V+FF and initiators of other single-device ICS+LABA combination therapies among 12-17-year-old individuals with asthma during a two-year follow-up was compared using an active comparator new-user design in Finnish national healthcare registers (2017-2023) and Clinical Practice Research Database (CPRD Aurum, 2016-2024) from UK. The primary estimand assessed the hazard ratio (HR) of pneumonia while alive and on treatment (i.e., before treatment discontinuation or switching to another ICS+LABA combination), regardless of using other add-on or rescue medications. The primary analysis used a weighted Cox regression with inverse probability of treatment-weighting (IPTW). Sensitivity analyses

	varying the conditions defining the censoring at random assumption with inverse probability of censoring weighting (IPCW) or tipping point analyses, as well as the impact of non-differential exposure misclassification were conducted. Supplementary estimands evaluated the difference in restricted two-year mean survival time to pneumonia for V+FF vs. other ICS+LABA combination, or the HR of pneumonia, including pneumonia deaths, for V+FF vs. other ICS+LABA combination, while alive and on treatment, regardless of using other add-on or rescue medications. **Results:** The study included 598 V+FF initiators and 2089 initiators of other ICS+LABA products from Finland and 596 V+FF initiators and 7790 other ICS+LABA initiators from the UK. The number of individuals was significantly smaller than the target sample size of 26,750 persons in both treatment groups, and the event counts were very low in both groups (<5 among V+FF initiators and 6 among other ICS+LABA initiators in UK CPRD, 6 and 12, in Finland). Median lengths of follow up were relatively short, 11 and 7 months in FinReg and 3.4 and 3.0 months in CPRD for users of V+FF and other ICS+LABA, respectively. In UK CPRD and FinReg, the adjusted HR for first pneumonia were 3.00 (95% CI 0.34–26.25) and 1.51 (95% CI 0.56-4.08) respectively among V+FF initiators compared with other ICS+LABA initiators. The pooled primary estimand HR 1.70, 95%CI 0.69-4.20 from Finland and CPRD also does not indicate an increased pneumonia risk in adolescents with asthma who initiate single-device V+FF compared to other ICS+LABA combination. The sensitivity analyses of estimand 1, exploring the robustness of results for extreme missing data assumptions were consistent with the main analyses except for the scenario maximally favouring the comparison group that suggested increased HR of pneumonia in the V+FF group. However, this was observed only in CPRD (HR, 95%CI 25.17, 9.39-67.46) where the number of nonadministrative censored people was larger than in FinReg, and the follow-up time was shorter and number of outcome events lower than in FinReg. The scenario maximally favouring V+FF suggested a lower hazard of pneumonia in V+FF initiators in CPRD (HR, 95%CI 0.90, 0.37-2.17) but not in FinReg. The sensitivity analyses for exposure misclassification could be conducted in FinReg only, due to low event rate in UK CPRD, and the results in FinReg were consistent with the main analyses (1.59, 0.59-4.29). Sensitivity analysis for nondifferential exposure misclassification could not be calculated for UK CPRD due to masking of small event counts. Therefore sensitivity analyses were not conducted for the pooled results either. In Finland the results of

	sensitivity analysis accounting for nondifferential exposure misclassification were in line with the main analysis (IPTW HR, 95%CI 1.59, 0.59-4.29). Estimand 2 analyses were hampered by small number of events and could not be conducted in CPRD. In FinReg the RMST was 1.98 months in the V+FF group and 1.99 in the comparison group, with no difference in the mean RMST between the groups (-0.01, 95% CI-0.03 to 0.01 months). Estimand 3 was not estimated due to identical censoring distribution and number of events to the primary estimand as no deaths occurred in the study population, **Conclusion:** In this non-interventional study using target trial emulation and the estimands framework, the results do not provide evidence of the existence or absence of a difference in pneumonia risk among adolescent asthma patients who initiate V+FF instead of other ICS+LABA combinations. The number of adolescents initiating V+FF during the study period was lower than anticipated, resulting in smaller-than-planned study populations, low event rates, and limited precision of the estimated effects. These limitations also affected the interpretation of some sensitivity analyses. These findings demonstrate that for special groups such as paediatric or adolescent populations and rare outcomes as pneumonia, inclusion of multiple countries and longer follow-up time is needed to ensure sufficient number of exposed participants in new-user designs and sufficient number of events, even for common conditions among paediatric or adolescent populations such as asthma. The combination of target trial emulation and estimand frameworks informed the framing of a regulatory-relevant research question with supportive sensitivity and secondary analyses to investigate key assumptions. However, the low number of events restricted the ability to make meaningful comparisons across the results.

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4. Abbreviations

Abbreviation	Definition
AFT	accelerated failure time
CPRD	Clinical Practice Research Database
COPD	chronic obstructive pulmonary disease
DEAP	Data Expert and Access Partner
DRE	Digital Research Environment
ED	emergency department
HR	Hazard Ratio
ICS	inhaled corticosteroid
IP	inpatient
IPTW	Inverse Probability of Treatment Weighting
IPCW	inverse probability of censoring weighting
LABA	long-acting beta-2 adrenoceptor agonist
NR	not reportable (due to low frequency)
OP	outpatient
RMST	restricted mean survival time
SABA	short-acting beta2-agonists
SAMA	short-acting muscarinic receptor antagonist
TTE	Target Trial Emulation

V+FF	vilanterol-fluticasone furoate

5. Protocol Amendments

Table 1. Protocol amendments

Version date	Version number	Section of protocol	Amendment or update	Reason
27 February 2026	1.0			
3 June 2026	2.0	7.3.1 Definition of time 0 for entry to the study population - context and rationale	The following text was added: *"The study is conducted as a single-entry study, meaning that if a person has multiple qualifying entries, only the first one is considered."*	The change clarifies that subjects can contribute only once to the study.
		Table 10	Split *"end of observation data"* into *"Date of final data capture in data source"* and *"End date of individual observation in the data source (e.g., migration or de-registration from the practice)"* End of exposure: *Censoring at end of exposure occurs when the participant had no subsequent dispensing/ prescription within 30 days after the calculated end of the previous dispensing's/ prescription's duration, with follow-up ending 30 days after the final prescription coverage period."*	The definition of end of observation was not sufficiently specific, as it could occur through two distinct mechanisms. Specification how the end of exposure is defined and occurrence of censoring at end of exposure.

Version date	Version number	Section of protocol	Amendment or update	Reason
			Treatment switch: "*Censoring occurs at the dispensing/prescription of the other ICS+LABA combination."*	Specification of switching event and occurrence of censoring at that event.
		Table 11	*"Number of Outpatient visits"* changed to *"number of primary care visits".* Variable type of ICS dose changed from *"continuous"* to *"categorical"*	Specification of healthcare setting. The variable in the database is categorical.
		Annexes	Addition of the study code list as annex	Inclusion of the study code list for programming activities to identify eligibility criteria, exposures, outcome, covariates, etc., which was missing.

6. Background

Vilanterol is an ultra-long-acting beta 2-adrenoceptor agonist indicated for chronic obstructive pulmonary disease (COPD) and asthma. Fluticasone furoate is a corticosteroid, available in nasal and inhaled administration forms with different indications. Vilanterol-fluticasone furoate (V+FF) combination treatment is indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of inhaled corticosteroid-long-acting beta-2 adrenoceptor agonist combination (ICS+LABA combination) is appropriate, i.e. adequate symptom control is not achieved with ICS and as-needed short-acting beta2-agonists (SABA), or for patients already adequately controlled on ICS+LABA combination).

Pneumonia is a severe infection, and its impact on patients with asthma can be particularly harmful due to underlying conditions. In 2016, the Pharmaceutical Risk Assessment Committee of European Medicines Agency concluded that the association between ICS and pneumonia observed in COPD patients is likely causal.[2] Since then, this association has been reported in asthma cohorts, including a cohort study of adolescents and young adults (age 12-35 years).[3] Pneumonia has been included in the pre-specified adverse events in randomised controlled trials on asthma treatment, but there are no specific estimates on pneumonia risk in adolescents with asthma. Higher pneumonia rates for patients on V+FF combination treatment in comparison to ICS have been reported in trials on adolescent and adult asthma patients.[1,4] However, the number of adolescent patients in these trials was limited, so the risk increase in this population is not known.

Therefore, the aim of this study was to evaluate the risk of pneumonia in V+FF initiators in comparison to other ICS+LABA single-device treatments in representative real-world settings among adolescents with asthma who are already on ICS treatment. We employed two European national databases routinely used for research purposes: Finnish national healthcare registers and Clinical Practice Research Database (CPRD) from UK. Both data sources include inpatient and outpatient diagnosis and procedure data. The Finnish data covers dispensations in outpatient settings whereas CPRD captures prescriptions in outpatient settings.

7. Research questions and objectives

The overall aim is to assess whether the risk of incident pneumonia differs between V+FF combination initiators compared with initiators of other single-device combination treatments.

7.1. *Primary Estimand 1*

Table 2. Primary Estimand (Estimand 1)

	Target Trial	Target Trial Emulation (TTE)	Comment
Population	Adolescent patients with asthma already treated with ICS	Adolescent patients with asthma already treated with ICS	
Treatment Conditions	Intervention:vilanterol-fluticasone furoate Control: other single-device ICS+LABA combinations (not vilanterol-fluticasone furoate)	Intervention: vilanterol-fluticasone furoate Control: other single-device ICS+LABA combinations (not vilanterol-fluticasone furoate)	Intervention and control identified from prescriptions in electronic health records/national prescription databases using ATC/DM+D codes. Exposure based on first observed prescription after one-year washout.
Endpoint	Time to pneumonia	Time to pneumonia, identified with ICD-10/Read codes using electronic health records/national registers (diagnoses from primary and secondary care)	Majority of events in trials are outpatient-treated -> outpatient diagnosis data in TTE necessary and available for both data sources. Emulated using validated code lists.
Summary Measure	Hazard ratio	Hazard ratio	
Intercurrent events and strategies to handle them	Same for both treatment conditions Discontinuation: while on treatment	Intercurrent events are handled according to pre-specified strategies of the hypothetical target trial Treatment discontinuation is defined as a gap of more than 30 days between the coverage of consecutive prescriptions for the index therapy (ATC/DM+D code). Switches are considered as a	Inaccuracies in estimation of timepoint of discontinuation are anticipated due to reliance on prescription data.

	Target Trial	Target Trial Emulation (TTE)	Comment
		specific form of discontinuation and defined as initiation of another ICS+LABA treatment during continuous treatment of the index therapy.	
	Add-on/rescue medications: treatment policy	Add-on/rescue medications, including dose adjustments of ICS or LABA of the index therapy are determined by prescriptions of these medications during continuous treatment with index therapy.	Whilst add-on and rescue medication rely on the accuracy of prescribing records, the impact of such inaccuracies is less important because in treatment policy approach individuals are followed regardless of whether they experience the intercurrent event.
	Death (any cause): while alive	Death dates are identified from population register or electronic health records.	Deaths are expected to be rare in this patient population, and there is a possibility of misclassification (some of the deaths may be due to pneumonia). Information on causes of death is not available in both database instances.

Research question answered by the estimand: What is the HR of pneumonia for V+FF vs. other ICS+LABA combination in adolescent asthma patients who were on ICS treatment within the year preceding the initiation, while alive and on treatment (i.e., before treatment discontinuation or switching to another ICS+LABA combination), regardless of using other add-on or rescue medications?

Rationale for handling of intercurrent events: The risk of pneumonia is a safety concern plausible when patients are exposed to the study treatments. While-on-treatment strategy for switches and discontinuations estimates the effect of treatment exposure during the period when patients use the medicine. Treatment policy strategy for other add-on medications and rescue medications such as biologicals reflects usual clinical practice. Deaths are a rare intercurrent event in the young study population and causes of death information are not available from both study sites. In addition, pneumonia deaths in this population are likely preceded by admission so outcome misclassification is likely to be rare.

7.2. *Supplementary Estimand 2*

Table 3. Secondary Estimand (Estimand 2)

	Target Trial	Target Trial Emulation (TTE)	Comment
Population	As in Estimand 1		
Treatment Conditions	As in Estimand 1		
Endpoint	As in Estimand 1		
Summary Measure	Difference in restricted mean survival time	Difference in restricted mean survival time	
Intercurrent events and strategies to handle them	As in Estimand 1		

Research question answered by the estimand: What is the difference in restricted (at two years) mean survival time to pneumonia for V+FF vs. other ICS+LABA combination in adolescent asthma patients who were on ICS treatment within the year preceding the initiation, while alive and on treatment (i.e., before treatment discontinuation or switching to another ICS+LABA combination), regardless of using other add-on or rescue medications?

Rationale for handling of intercurrent events: The risk of pneumonia is a safety concern plausible when patients are exposed to the medicines of interest. While-on-treatment strategy for switches and discontinuations estimates the effect of treatment exposure during the period when patients use the medicine. Treatment policy strategy for other add-on medications and rescue medications such as biologicals reflects usual clinical practice. Deaths are a rare intercurrent event in the young study population and causes of death information are not available from both study sites. In addition, pneumonia deaths in this population are likely preceded by admission so outcome misclassification is likely to be rare.

7.3. *Supplementary Estimand 3*

Table 4. Tertiary Estimand (Estimand 3, for Finland only)

	Target Trial	Target Trial Emulation (TTE)	Comment
Population	As in Estimand 1		
Treatment Conditions	As in Estimand 1		
Endpoint	Time to pneumonia diagnosis or pneumonia death	Time to pneumonia diagnosis of death due to pneumonia, identified with ICD-10 codes using national registers (diagnoses from primary and secondary care and causes of death).	Causes of death added as a source of case ascertainment.
Summary Measure	Hazard ratio	Hazard ratio	
Intercurrent events and strategies to handle them	Otherwise as in Estimand 1, except Pneumonia death: composite. Non-pneumonia death: while alive	Death dates and causes of death are identified from the causes of death register.	Deaths are expected to be rare intercurrent events, and there is a possibility of misclassification. For this estimand, pneumonia cases ascertained from causes of death register in addition to primary and secondary healthcare data. In addition, instead of any cause death, the intercurrent event of death is restricted to non-pneumonia deaths.

Research question answered by the estimand: What is the HR of pneumonia, including pneumonia deaths, for V+FF vs. other ICS+LABA combination in adolescent asthma patients who were on ICS treatment within the year preceding the initiation, while alive and on treatment (i.e., before treatment discontinuation or switching to another ICS+LABA combination), regardless of using other add-on or rescue medications?

Rationale for handling of intercurrent events: The risk of pneumonia is a safety concern plausible when patients are exposed to the medicines of interest. While-on-treatment strategy for switches and discontinuations estimates the effect of treatment exposure during the period when patients remain adherent. Treatment policy strategy for other add-on medications and rescue medications such as biologicals reflects usual clinical practice. Ascertaining pneumonia cases also from causes of death register and including non-pneumonia deaths as an intercurrent event assists in evaluating the impact of misclassification bias on estimand 1.

8. Research methods

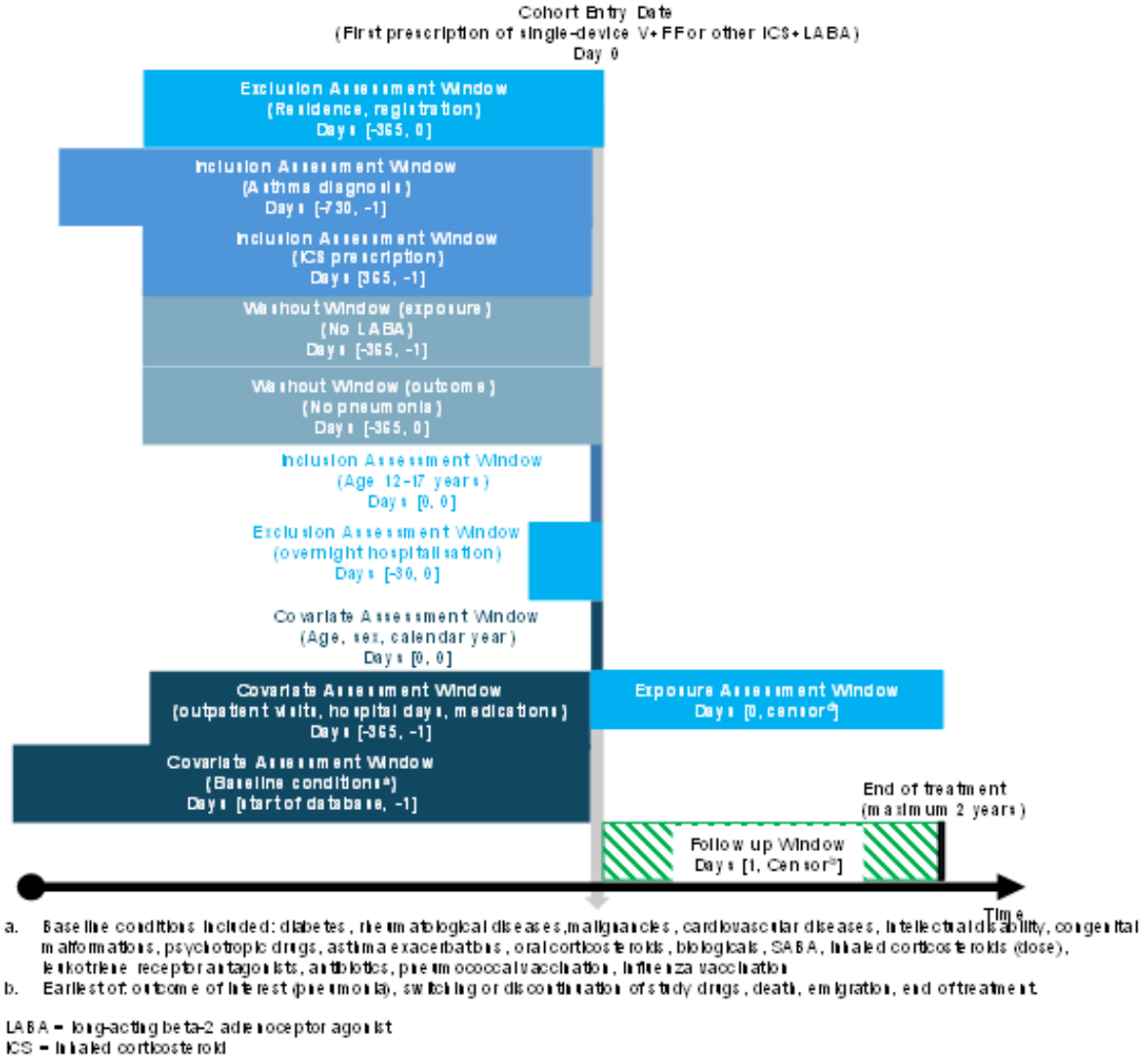
8.1. *Study design*

Research design: Active comparator new user cohort design.

Rationale for study design choice: The active comparator study design reduces risk of bias from unmeasured confounding by indication and is optimal for the target trial emulation framework. Using another single-device ICS+LABA combination treatment reduces indication bias, and restriction to single-device treatments ensures similar compliance between the treatment arms. The comparison treatments are clinically relevant and commonly prescribed alternative to V+FF. In an observational setting, comparison to ICS only would be confounded by asthma severity, which would not be sufficiently captured by the available data.

The new-user design ensures easily identifiable and comparable time 0 between treatment arms as the follow-up starts with treatment initiation. This avoids immortal time bias, which can occur if follow-up starts before the actual initiation of therapy.

8.2. *Study design diagram*



a. Baseline conditions included: diabetes, rheumatological diseases, malignancies, cardiovascular diseases, intellectual disability, congenital malformations, psychotropic drugs, asthma exacerbations, oral corticosteroids, biologicals, SABA, inhaled corticosteroids (dose), leukotriene receptor antagonists, antibiotics, pneumococcal vaccination, influenza vaccination

b. Earliest of: outcome of interest (pneumonia), switching or discontinuation of study drugs, death, emigration, end of treatment

LABA = long-acting beta-2 adrenoceptor agonist
ICS = inhaled corticosteroid

Figure 1. Study design diagram

8.3. *Setting*

This study is conducted using routinely collected electronic health records from 2014 to 2023. The study is set primarily in primary care, drawing on longitudinal data from general practices with linkage to hospital data. Data are sourced from two European countries, the United Kingdom (Clinical Practice Research Datalink [CPRD]) and Finland (Finnish national registries), providing population-based and representative coverage of real-world clinical care.

8.3.1. Definition of time 0 (and other primary time anchors) for entry to the study population

Time 0 is the date of initiation of V+FF or other single-device ICS+LABA combination treatment. This is when the adolescent asthma patients who fulfil the eligibility criteria enter the study population and it mimics the timing of initiation of therapy at randomisation in the target trial. The study was conducted as a single-entry study, meaning that if a person had multiple qualifying entries, only the first one was considered.

Table 5. Operational Definition of Time 0 (index date) and other primary time anchors

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Exposure: single-device V+FF	Date of incident prescription/ dispensation for V+FF (time 0)	Single	Incident	[-365, -1]	OP	ATC DM+D	n/a	LABA (any formulation)		Investigator review of ATC/DM+D codes
Comparator: other single-device ICS+LABA	Date of incident prescription/ dispensation for ICS+LABA (time 0)	Single	Incident	[-365, -1]	OP	ATC DM+D	n/a	LABA (any formulation)		Investigator review of ATC/DM+D codes

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2]See appendix for listing of clinical codes for each study parameter

8.3.2. Study inclusion criteria

Inclusion Criteria

One year of residence or registration in the relevant database prior to time 0 was required to ensure that the study participants had observable time in the data with healthcare system contacts to allow capture of clinical codes to measure inclusion and exclusion criteria and covariates. We restrict the population to adolescents aged 12-17 years to evaluate pneumonia risk in adolescent asthma population. All participants were required to have a dispensed (Finland) or written (UK) ICS prescription within the year preceding time 0 to ensure they had a step up of asthma treatment (from maintenance ICS and as needed SABA). All participants were required to have at least one dispensation (Finland) or written prescription (UK) of V+FF or other ICS+LABA single-device combination treatment.

Table 6. Operational Definitions of Inclusion Criteria

Criterion	Details	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/validation	Source for algorithm
At least one dispensation or written prescription of V+FF or other single-device ICS+LABA		[0, 0]	OP	ATC DM+D	n/a	Exposure: single-device V+FF Comparator: other single-device ICS+LABA		
Observable time	Continuous residence/ registration in database	[-365, 0]	n/a	n/a	n/a	Exposure: single-device V+FF Comparator: other single-device ICS+LABA		n/a
Age 12-17 yrs		[0, 0]	n/a	n/a	n/a	Exposure: single-device V+FF Comparator: other single-device ICS+LABA		n/a
Asthma diagnosis	Based on diagnostic and special reimbursement codes	[-730, -1]	Any	ICD-10, special reimbursement, Read	Any	Exposure: single-device V+FF Comparator: other	references [5,6]	

Criterion	Details	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/validation	Source for algorithm
						single-device ICS+LABA		
ICS treatment	Based on record of prescription and/or dispensing	[-365, -1]	OP	ATC DM+D	n/a	device V+FF Comparator: other single-device ICS+LABA		

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

8.3.3. Study exclusion criteria

Exclusion Criteria

We excluded participants with overnight hospitalisation within 30 days prior to day 0 to exclude those with possible recent asthma exacerbations, that were directly recorded in the applied real-world data sources, and to avoid incorrect specification of day 0 as they may have been administered ICS+LABA while in hospital, because information in hospital-administered treatments was not available in the applied data sources. Records with missing values for key demographic variables (e.g., age or sex) were excluded from the analysis as information for these individuals was not provided by the database maintainers at the data extraction stage.

Table 7. Operational Definitions of Exclusion Criteria

Criterion	Details	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Previous pneumonia	Based on diagnostic codes	[-365, 0]	Any	ICD-10 Read/SNOMED	Any	Exposure: single-device V+FF Comparator: other single-device ICS+LABA		
Overnight hospitalisation	Based on recorded hospital stay	[-30, 0]	IP	n/a	n/a	Exposure: single-device V+FF Comparator: other single-device ICS+LABA		

[1]IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2]See appendix for listing of clinical codes for each study parameter
[3]Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

8.4. *Variables*

8.4.1. Exposure(s) of interest

The use of an active comparator of other single-device ICS+SABA combination treatment allows the comparison of initiators in need of a similar line of therapy and at a similar stage of asthma severity, reducing confounding by indication. Restriction to single-device treatment ensures similar compliance between the treatment groups.

Algorithm to define duration of exposure effect:

The study medications are single-inhalation once-daily administration so fixed assumptions method using one dose/day based on dispensed amount was used to construct treatment episodes. A 30-day grace period between calculated duration of prescriptions was used to account for noncompliance. For the last prescription, duration was calculated based on the dispensed amount and a carryover period of 30 days was added. This was based on the half-life of ICS (2-3days) and possible delay in clinical manifestation and diagnosis of pneumonia.

Table 8. Operational Definitions of Exposure

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Exposure	Single-device V+FF based on record of prescription and/or dispensing	[-365, -1]	[0, censor]	OP	ATC DM+D	n/a	All study populations	Prescriptions measured in one year prior to first use	reference[7]	Investigator review of available products in study countries
Comparator	Other single-device ICS+LABA based on record of prescription and/or dispensing	[-365, -1]	[0, censor]	OP	ATC DM+D	n/a	All study populations	Prescriptions measured in one year prior to first use	reference[7]	Investigator review of available products in study countries

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

8.4.2. *Outcome(s) of interest*

Pneumonia is a severe infection, and its impact on patients with asthma can be particularly harmful due to underlying conditions. Pneumonia also increases the risk of asthma exacerbations in all age groups, and ICS increase the risk of pneumonia also in adolescents. Pneumonia has been included in the pre-specified adverse events in asthma RCTs, but there are no specific estimates on pneumonia risk in the adolescent population. Most pneumonia cases are treated in outpatient settings. Therefore, we include both in- and outpatient diagnoses as well as data from primary and secondary healthcare.

Table 9. Operational Definitions of Outcome

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
Pneumonia	Diagnosis date from primary or secondary healthcare. In estimand 3 death date from causes of death register is used in addition to diagnosis date.	Yes	Time-to-event	[-365, 0]	OP, IP	ICD-10 Read SNOMED	any	Exposure: single-device V+FF Comparator: other single-device ICS+LABA		investigator review of codes

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

8.4.3. Follow-up

The investigated medications are intended for long-term period of use as asthma is a chronic condition. However, significant changes in asthma severity and symptoms occur in puberty, and a significant proportion of even severe asthma cases are resolved during adolescence,[8] supporting the restriction of study duration to two years. A duration of 2 years is expected to be sufficient for capturing enough pneumonia events.

Table 10. Operational Definitions of Follow Up

Follow up start	Day 1	
Follow up end[1]	**Select all that apply**	**Specify**
Date of outcome	Yes	First occurrence of pneumonia
Date of death	Yes	Date of any death (estimands 1,2) Date of non-pneumonia death (estimand 3)
Date of final data capture in data source	Yes	Censor at database end; administrative censoring
End date of individual observation in the data source (e.g., migration or leaving the practice	Yes	Censor at date of emigration or known deregistration; Non-administrative censoring
Day X following index date *(specify day)*	Yes	Day 730; administrative censoring
End of study period (specify date)	Yes	31-Dec-2023
End of exposure *(specify operational details, e.g. stockpiling algorithm, grace period)*	Yes	Fixed assumption method (1 dose per day) with 30-day grace period. Censoring at end of exposure occurs when the participant had no subsequent dispensing/prescription within 30 days after the calculated end of the previous dispensing's/prescription's duration, with follow-up ending 30 days after the final prescription coverage period.
Date of switch from exposure *(specify algorithm)*	Yes	Initiation of another ICS+LABA combination during continuous treatment of the index therapy based on prescription data. Censoring occurs at the dispensing/prescription of the other ICS+LABA combination.
Other date *(specify)*	No	

[1] Follow up ends at the first occurrence of any of the selected criteria that end follow up.

8.4.4. Covariates

The study covariates were chosen based on previous literature on risk factors for pneumonia, asthma severity and outcomes in asthma. These include age, sex, season, diabetes, rheumatological diseases, malignancies, cardiovascular diseases, intellectual disability, congenital malformations, psychotropic drugs, asthma exacerbations, oral corticosteroids, biologicals, SABA, SAMA, inhaled corticosteroids dose before the index date, leukotriene receptor antagonists, antibiotic use, pneumococcal vaccination, influenza vaccination. In addition, calendar year was used to account for possible time trends, and number of outpatient admissions and hospital days are used as proxies for overall comorbidity.

Table 11. Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings [1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics / validation	Source for algorithm
Age	(cohort entry date - date of birth) in years. Accuracy for DOB varies between databases (year/month/exact date)	Continuous	[0,0]	n/a	n/a	n/a	Exposure: single-device V+FF Comparator: other single-device ICS+LABA		
Sex	men, women	Binary	[0,0]	n/a	n/a	n/a	as above		
Calendar year		Categorical	[0,0]	n/a	n/a	n/a	as above		
Season	month or as 4 categories	Categorical	[0,0]	n/a	n/a	n/a	as above		
Number of primary care visits		Continuous	[-365,-1]	OP	n/a	n/a	as above		
Number of hospital days		Continuous	[-365,-1]	IP	n/a	n/a	as above		
diabetes		Binary	[-start of database,-1]	OP,IP	ICD-10 Read SNOMED	any	as above		

Characteristic	Details	Type of variable	Assessment window	Care Settings [1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics / validation	Source for algorithm
					ATC DM+D				
rheumatological diseases		Binary	[-start of database,-1]	OP,IP	ICD-10 Read SNOMED	any	as above		
malignancies		Binary	[-start of database,-1]	IP	ICD-10 Read SNOMED	any	as above		
other immunological conditions		Binary	[-start of database,-1]	IP	ICD-10 Read SNOMED	any	as above		
cardiovascular diseases		Binary	[-start of database,-1]	OP,IP	ICD-10 Read SNOMED ATC DM+D	any	as above		
intellectual disability		Binary	[-start of database,-1]	OP,IP	ICD-10 Read SNOMED	any	as above		
congenital malformations		Binary	[-start of database,-1]	OP,IP	ICD-10 Read SNOMED	any	as above		
psychotropic drugs		Binary	[-365,-1]	OP	ATC DM+D	any	as above		
Asthma exacerbations	Number of asthma-related hospitalisations	Continuous	[-365,-1]	IP	ICD-10, Read SNOMED	main	as above		
oral corticosteroids		Binary	[-365,-1]	OP	ATC DM+D	any	as above		
biologicals		Binary	[-365,-1]	OP	ATC DM+D	any	as above		
SABA		Binary	[-365,-1]	OP	ATC DM+D	any	as above		
Short-acting muscarinic antagonists (SAMA)		Binary	[-365,-1]	OP	ATC DM+D	any	as above		
Inhaled corticosteroids (dose)	obtained from the latest prescription before the index date	Categorical	[-365,-1]	OP	ATC DM+D	any	as above		

Characteristic	Details	Type of variable	Assessment window	Care Settings [1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics / validation	Source for algorithm
leukotriene receptor antagonists		Binary	[-365,-1]	OP	ATC DM+D	any	as above		
antibiotic use		Binary	[-365,-1]	OP	ATC, DM+D	any	as above		
pneumococcal vaccination		Binary	[-365,-1]	OP	ATC DM+D	any	as above		
influenza vaccination		Binary	[-365,-1]	OP	ATC DM+D	any	as above		

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

8.5. *Core Emulation Table(s) - Design Summary*

Table 12. Comparison of Target Trial and Proposed Target Trial Emulation Design Elements (Estimand 1)

	Target Trial	Target Trial Emulation	Comment
Inclusion criteria	1. age 12-17 years at randomisation 2.diagnosis of asthma 3.step-up to ICS+LABA combination necessary because asthma symptoms not adequately controlled with current treatment	1. age 12-17 years at initiation V+FF or comparison medication 2. asthma diagnosis within 730 days before initiation 3. previous ICS treatment within 365 days of initiation 4. a first prescription of V+FF or other single-device ICS+LABA combination treatment The target trial is emulated using data on people included in EHR/national registers.	Emulation study population is restricted to new users of the medicines of interest. The necessity for adding LABA to current treatment is assumed to represent a step-up from having symptoms insufficiently controlled with low-dose ICS (with/without SABA) but symptoms or disease control cannot be directly evaluated from patient records.

	Target Trial	Target Trial Emulation	Comment
Exclusion criteria	1. previous pneumonia diagnosis within the previous year 2.LABA treatment within the previous year 3.hospitalisation within 30 days prior to randomisation.	1.ICD-10/Read diagnosis of pneumonia in primary care/secondary care EHR 365 days before initiation of study therapy 2.ATC/DM+D code for LABA in dispensing data in 365 days before initiation of study therapy 3.Overnight hospitalisation in 30 days before initiation of study therapy	Inaccuracies in diagnostic coding can affect the ability to capture the exclusion criteria in the emulation study
Setting	Treatment in outpatient setting, outcomes from in- and outpatient care	Electronic healthcare record data sources capturing prescriptions/dispensations, outcomes, and covariates capturing treatment in outpatient setting, outcomes from in- and outpatient care	
Method of Assignment to Trial Intervention	Randomisation	Assignment reflects clinical need.	Randomisation cannot be directly emulated. In the statistical analysis, inverse probability of treatment weighting following propensity score calculation will be used to balance baseline covariates to emulate randomisation.
Study treatment conditions	Intervention: vilanterol- fluticasone furoate. Control: other single-device ICS+LABA combinations (not vilanterol-fluticasone furoate)	Intervention: vilanterol- fluticasone furoate. Control: other single-device ICS+LABA combinations (not vilanterol-fluticasone furoate) Medications are identified using ATC/DM+D codes.	Intervention and control identified from prescriptions or dispensing in electronic health records/national prescription databases using ATC/DM+D codes. Exposure based on first observed written (UK) or dispensed (Finland) prescription.
Time *(when follow up begins and ends):*	Starts at randomisation, ends at pneumonia, death, treatment discontinuation, study withdrawal, loss to follow-up, or trial end (two years after randomisation), whichever occurs first	Starts at initiation of V+FF or comparator, ends at pneumonia, death, treatment discontinuation, loss to follow-up or two years since treatment initiation, whichever occurs first	In estimands 1 and 2, all deaths regardless of cause are intercurrent events. In estimand 3, non-pneumonia deaths are intercurrent events, but pneumonia deaths are included as pneumonia. First prescription/dispensation is used as a proxy for initiation.

	Target Trial	Target Trial Emulation	Comment
Outcome (including operational definition)	Pneumonia	Pneumonia diagnosis in primary or secondary care based on ICD-10/Read/SNOMED code (primary diagnosis)	Causes of death are not available from CPRD. Therefore, primary analyses (estimands 1 and 2) are conducted with any death as an intercurrent event. Most of the fatal pneumonia events in this population are expected to be preceded by pneumonia hospitalization, therefore the fatal cases are likely to be captured with the EHRs. To evaluate the impact of potential misclassification, pneumonia deaths are included in the outcome for estimand 3, which will only be estimated using Finnish data.
Intercurrent Events and strategies to handle them	1. Treatment discontinuation 2.Add-on/rescue medications 3.Death, any cause (estimands 1-2) Non-pneumonia death (estimand 3)	1. Assessed based on dispensing (dispensing dates, ATC/DM+D codes and dispensed quantity): while on treatment strategy 2. Identified with dispensing information (ATC/DM+D codes): treatment policy strategy 3. Identified from population register or EHR: while alive strategy Identified from causes of death register: while alive strategy	Treatment start and end dates must be estimated in the datasets as precise times are not provided.
Loss to follow up	Patients who fail to return for the required study visits and his/her health condition and vital status remains unknown despite multiple attempts to contact them.	Patients with known deregistration or emigration date or database end. Measured directly in data sources	Information on emigration/registration end dates are available in both data sources. Real-world proxy used to define loss to follow-up;

Estimand 2

Same as estimand 1 but difference in restricted mean survival time instead of hazard ratio is used as the summary measure.

Estimand 3 (Finland only)

Same as estimand 1 but pneumonia cases ascertained from causes of death register in addition to primary and secondary healthcare data. In addition, instead of any cause death, the intercurrent event of death is restricted to non-pneumonia deaths.

8.6. *Data analysis*

8.6.1. Analysis Plan

Overview

The analyses were conducted within a target trial emulation framework to estimate the effect of initiating single-device V+FF vs. other single-device ICS+LABA on the risk of incident pneumonia.

For **Estimand 1**, the main estimand supporting decision making, the primary analysis is an IPTW-weighted Cox proportional hazards model. Sensitivity analyses assessing the robustness of the results to assumptions in censoring assumptions and nondifferential exposure misclassification made in the primary analysis with including inverse probability of censoring weighting (IPCW), tipping point analysis, and probabilistic bias analysis for non-differential exposure misclassification.

Supplemental analyses include diagnostic and descriptive assessments to support the main analysis. These cover crude and IPTW-adjusted Kaplan-Meier curves, crude Cox models, event counts, incidence rates, weight and propensity score distributions, covariate balance before and after weighting, censoring and intercurrent event patterns, proportional hazards diagnostics, and positivity checks.

Separate Cox regression models for each data source were fitted and the estimated HRs from Finland and CPRD were combined with a random effects meta-analysis of log hazard rations with IPTW. The estimate agreement between the data sources will be assessed as outlined by Franklin et al.[9]

Two supplemental estimands were also defined: **Estimand 2**, estimating treatment effects using restricted mean survival time (RMST) derived from an IPTW-weighted Weibull accelerated failure time (AFT) model and **Estimand 3** (in Finnish data only), investigating time to first pneumonia diagnosis or pneumonia death with same statistical analysis methods as in Estimand 1.

8.6.2. Primary Estimand Analysis

i. Objective

To estimate the hazard ratio of incident pneumonia in initiators of V+FF versus other single-device ICS+LABA.

ii. Exposure contrast

Single-device V+FF vs. other single-device ICS+LABA

iii. Outcome

Time to first pneumonia diagnosis

iv. Software

R.

v. Handling of intercurrent events

Handle intercurrent events according to the following strategies:

- Treatment discontinuation (both or an individual component): Apply a while-on-treatment strategy
- Treatment switching: Apply a while-on-treatment strategy.
- Add-on or rescue medications: Apply a treatment policy strategy
- Death: Apply a while-alive strategy

For the intercurrent events handled with a "while…" strategy, data will be excluded after the occurrence of the intercurrent event.

For intercurrent events handled with a treatment policy strategy data after the occurrence of the intercurrent event will be included in the analysis.

vi. Outcome Modelling

An IPTW Cox proportional hazards model was used to estimate the effect of initiating V+FF versus other single-device ICS+LABA on time to first pneumonia diagnosis

Start of follow-up: date of treatment initiation for single-device V+FF or other single-device ICS+LABA

- Timescale: time since index date
- Endpoint: first occurrence of pneumonia
- Censoring:
    - Non-administrative censoring: Loss to follow-up
    - Administrative censoring: End of study follow-up in the absence of pneumonia (end of data instance; FinReg 31.12.2023, UK CPRD 16.9.2024 or maximum two years)
    - Model covariate: Treatment group (single-device V+FF or other single-device ICS+LABA)

Assumptions of KM

- Non-informative Censoring:

- For Crude KM curves: Censoring is assumed to be independent of the outcome, conditional on treatment and survival up to the time of censoring.
- For IPTW-adjusted KM: Censoring is assumed to be independent of the outcome, conditional on the treatment, survival up to the time of censoring and indirectly baseline covariates used to estimate the treatment weights
- Times of events and censoring are known and correctly recorded
- Independence between observations

Assumptions of Cox Model

Proportional Hazards:

- The hazard ratio is assumed to be constant over time.

Non-informative Censoring:

- Censoring is assumed to be independent of the outcome, conditional on the treatment, survival up to the time of censoring and indirectly baseline covariates used to estimate the treatment weights
- Times of events and censoring are known and correctly recorded
- Independence between observations

Diagnostics for Cox Model

Proportional hazards assessed using log(-log) survival plots or Schoenfeld residuals

vii. Confounding Adjustment

Inverse Probability of Treatment Weighting (IPTW)

Propensity scores, defined as the probability of initiating single-device V+FF or other single-device ICS+LABA inhibitor were estimated using logistic regression. The model included baseline covariates selected a priori as potential confounders due to their identification as risk factors for the outcome (age, sex, season, diabetes, rheumatological diseases, malignancies, cardiovascular diseases, intellectual disability, congenital malformations, psychotropic drugs, asthma exacerbations, oral corticosteroids, biologicals, SABA, SAMA, inhaled corticosteroids dose before the index date, leukotriene receptor antagonists, antibiotic use, pneumococcal vaccination, influenza vaccination, calendar year of initiation, number of primary care admissions and hospital days). Restricted cubic splines were used to model continuous variables.

Stabilised weights were calculated by dividing the marginal probability of receiving the treatment actually received (i.e., the overall proportion treated in the study population) by the individual's estimated propensity score (i.e., the conditional probability of receiving their observed treatment). Weights were truncated at the 1st and 99th percentiles to limit the influence of extreme values. In FinReg we applied trimming at <0.05 and ≥0.6 to remove participants at the nonoverlapping parts of the distribution (n=2 for V+FF group and 10 for other ICS+LABA group).

Truncated stabilised IPTW weights were applied in the Cox proportional hazards model (weighted likelihood) to estimate the marginal treatment effect of V+FF vs. other ICS+LABA combination on time to first pneumonia.

Standard errors were estimated using robust sandwich variance estimators.

Assumptions Underlying IPTW

- **No unmeasured confounding** (all relevant baseline confounders are included in the propensity score model).
- **Positivity** (each individual has a non-zero probability of receiving either treatment, given their covariates).
- **Correct model specification** (the propensity score model is correctly specified [functional form, covariate inclusion]).
- **Consistency** (each individual's potential outcome under the observed treatment equals their actual outcome).

Diagnostics for IPTW

- Evaluation of weight distribution before truncation in different treatment groups
- Evaluation of baseline covariate distribution in different treatment groups before and after trimming
- Covariate balance: Check that baseline characteristics are balanced across treatment groups after weighting.
- Evaluate standardized mean differences (SMDs): SMDs < 0.1 will be considered acceptable.
- Positivity check: Plot the distribution of PS (histograms) and graphically evaluate overlap.
- Describe baseline covariate distribution before and after PS based population trimming.

viii. Missing Data handling

Missing Exposure Data: We assume that missing dispensing or prescription records for V+FF or other ICS+LABA reflect true treatment discontinuation after the end of previous dispensing/prescription, and not incomplete data capture or prescriptions issued outside the database.

Missing Outcome Data: The Cox proportional hazards model implicitly assumes censoring occurring at random, meaning that censored participants contribute time at risk up to the time of censoring and their censoring is unrelated to the outcome, conditional on model covariates and survival up to

the time of censoring (i.e., outcome data is missing at random under these assumptions). The absence of an outcome event during the observed follow-up is interpreted as no occurrence of pneumonia.

Missing Covariate Data: The absence of a disease diagnosis code will be interpreted as the absence of the corresponding condition. All covariates in this study are either completely recorded (e.g. age and sex), or are binary variables based on coded medications or diagnoses. Absence of codes for medication or disease diagnoses is assumed to mean the absence of the corresponding medication or condition.

As such, there will be no missing data for covariates, exposure or outcome.

8.6.3. Supplemental Estimand (2) Analysis

i.Objective

Estimate the effect of initiation single-device V+FF vs. other single-device ICS+LABA on the risk of pneumonia

ii.Exposure contrast

single-device V+FF vs. other single-device ICS+LABA

iii.Outcome

Time to incident pneumonia diagnosis

iv.*Software*

R.

v.Handling of intercurrent events (explaining how follow-up is handled post intercurrent event)

Same as 8.6.2

vi.Outcome Model

IPTW weighted Accelerated Failure Time (AFT) model, followed by estimation of Restricted Mean Survival Time (RMST) at fixed time point of two years

Covariate in the model will include treatment group.
Start of follow-up: Date of treatment initiation.
Timescale: Time since index date

Endpoint: Time from treatment initiation to incident pneumonia

Censoring and missing outcome data:
Non-administrative: loss to follow-up
Administrative: two-year study end

Model Assumptions:

- Survival times follow a Weibull distribution
- Non-informative censoring (conditional on included covariates and survival up to time t)
- Log-linear relationship between covariates and log survival time

Diagnostics:

- Log(-log(S(t))) vs log(t) should be linear Q-Q plot of residuals

To estimate the RMST at two years from the Weibull AFT model, we first use the model to obtain the predicted survival curve for each treatment group. The RMST is then calculated as the average survival time up to a fixed time point, which corresponds to the area under the survival curve between time zero and two years. Confidence intervals are estimated with bootstrapping (1000 samples, percentile-based 95% confidence intervals constructed from these 1000 bootstrap estimates).

- Fit the Weibull AFT model, which gives the shape and scale of the survival curve for each group.
- From this model, generate the predicted survival probability at each time.
- Integrate (i.e., add up) the survival probabilities from time 0 to 2 years. The result is the expected survival time lived within those windows.
- Compare the RMST values between treatment groups to obtain the difference in average survival time over two years.

vii.Confounding adjustment

Same as 8.6.2; IPTW will be incorporated into the AFT model to obtain estimates of RMST at year 2

viii.Missing Data Handling
Same as 8.6.2

8.6.4. Supplemental Estimand (3) Analysis

i.Objective

Same as 8.6.2

ii.Exposure contrast

Same as 8.6.2

iii.Outcome

Time to incident pneumonia diagnosis or pneumonia death.

iv.Software:

R.

v.Handling of intercurrent events (explaining how follow-up is handled post intercurrent event)

Same as 8.6.2 except non-pneumonia death instead of any death is used as an intercurrent event and handled with a while-alive strategy.

vi.Outcome Model

Same as 8.6.2

vii.Confounding adjustment

Same as 8.6.2

viii.Missing Data Handling

Same as 8.6.2

8.6.5. Sensitivity Analyses

Table 13. Sensitivity analyses – Varying conditions of the censoring at random assumptions using Inverse Probability of Censoring Weighting (IPCW)

Analysis Methods	This analysis will examine the impact of varying assumptions about the censoring-at-random condition. In the primary analysis we assumed censoring independent of the outcome, ***conditional*** on treatment group and survival up to the time of censoring (i.e., outcome data is missing at random conditional on observed exposure and outcome). In the IPCW analysis, we use inverse probability of treatment weights and inverse probability of censoring weights. This analysis assumes censoring is independent of the outcome, with all common causes of both the outcome and censoring being accounted for. Follow-up will be divided into equal 30-day intervals. At the start of each interval, we will update the information available on each study participant and assess whether they remain followed or have been censored (due to nonadministrative reasons). If they remain under observation, they contribute to the risk set for that interval. The time-specific weight component for each participant at each interval is calculated as the inverse estimated probability of remaining uncensored, given a set of baseline and time-updated covariates that could affect both censoring and the outcome Characteristics that could affect both censoring and the outcome include: baseline (age, sex, calendar year of initiation, number of outpatient admissions and hospital days) and time varying covariates (time since index treatment initiation, asthma exacerbations, oral corticosteroids, biologicals, SABA, SAMA, inhaled corticosteroids dose, leukotriene receptor antagonists, antibiotic use, pneumococcal vaccination, influenza vaccination, upper respiratory tract infections, antihistaminic use/allergic dermatological conditions) The time-specific weight component is calculated separately for each interval, and then these weight components multiplied together across all intervals of follow-up to give each participant's cumulative weight. The denominator probability will be estimated using pooled logistic regression models fit to the person-interval dataset. The model outcome is whether the participant was censored in that interval. Time will be modelled flexibly using restricted cubic splines. We will truncate the weights at prespecified percentiles (1st and 99th). The stabilised IPCW will be applied as time-varying weights in the Cox model for time to incident pneumonia. As the inverse probability of treatment weights (IPTW) are also used, the final analysis weights will be the product of IPTW and IPCW.
Assumptions	• Censoring is conditionally independent of the outcome given covariates (i.e., non-informative censoring/censoring at random, conditional on other covariates beyond those in the outcome model); outcome does not directly influence its own missingness Correct model specification and positivity (every individual has a non-zero probability of remaining uncensored at each time point given their covariates).

What is Being Varied?	The condition of the censoring at random assumption.
Why (Objective)	• To assess the robustness of the treatment effect estimate to violations of the censoring at random assumption. If results are stable across scenarios, confidence increases that findings are not driven by selection bias due to censoring.
Strengths	• IPCW adjusts for measured predictors of censoring. Offers a principled method for recovering unbiased estimates under nonrandom censoring.
Limitations	• IPCW is sensitive to model misspecification. • Cannot account for unmeasured factors affecting censoring. • Weighting can increase variance, especially if weights are unstable Sensitivity analyses rely on varying the assumptions of the primary analysis, but for censoring these assumptions cannot be verified from the observed data; their plausibility can be discussed, yet ultimately remains unknown.

Table 14. Sensitivity analyses – Informative Censoring

<table>
<tr><td>Analysis Methods</td><td>• Best/worst case scenarios. The goal is to assess the impact on the estimated treatment effect of selected censoring non-at-random assumptions. The assumptions chosen represent the 4 extremes of a tipping point sensitivity analysis.
• For non-administrative-censored individuals, repeat the analysis under four scenarios, assuming within each treatment group that a) all censored individuals had the outcome of interest at the censoring date and b) no censored individuals had the outcome of interest by the end of the study. This equates to the following scenarios
<table>
<tr><th>Scenario</th><th>Exposed Group (V+FF)</th><th>Unexposed Group (Other ICS + LABA)</th><th>Interpretation</th></tr>
<tr><td>1</td><td>Best case (lowest event rate)</td><td>Worst case (highest event rate)</td><td>Maximally favors V+FF</td></tr>
<tr><td>2</td><td>Worst case (highest event rate)</td><td>Best case (lowest event rate)</td><td>Maximally favors Other ICS + LABA</td></tr>
<tr><td>3</td><td>Best case</td><td>Best case</td><td>Optimistic for both groups</td></tr>
<tr><td>4</td><td>Worst case</td><td>Worst case</td><td>Pessimistic for both groups</td></tr>
</table></td></tr>
<tr><td>Assumptions</td><td>• All or none of the censored individuals had the outcome of interest.</td></tr>
<tr><td>What is Being Varied?</td><td>• The assumption made in the primary analysis that censoring is non-informative given treatment group and survival up to the time of censoring.</td></tr>
</table>

Why (Objective)	• To assess the robustness of the treatment effect estimate to violations of the non-informative censoring assumption made in the primary analysis. • If results are stable across scenarios, confidence increases that findings are not driven by selection bias due to informative censoring.
Strengths	• Enables the exploration of alternative assumptions about censoring. • Does not assume a certain structure of informative censoring. • Sets bounds on the extent of maximum possible bias due to informative censoring
Limitations	• Best/worst case scenarios are extreme assumptions

Table 15. Sensitivity analyses – Non-Differential Exposure Misclassification

Analysis Method	Probabilistic Bias Analysis using Monte Carlo Simulation at the summary level measure. The final effect estimate from the main analysis will be used as the input for this analysis. The aim is to evaluate the potential impact of exposure initiation misclassification at index date (all prescriptions in CPRD may not be dispensed (primary adherence) or eventually used (secondary adherence), and all dispensations in the Finnish data may not be eventually used). This sensitivity analysis addresses misclassification of treatment initiation only (i.e., at index date), not exposure discontinuation or adherence during follow-up. • Probability distributions will be specified for the sensitivity and specificity parameters of exposure (i.e., treatment initiation) classification Plausible parameter ranges for prescription-based exposure measurement in real-world data (based on literature review of studies mainly assessing ICS use in adolescents); the adherence over the course of treatment was 49-71%[10] . However, as we are assessing initiations of ICS+LABA which typically represent intensification of treatment, we expect the adherence to be higher, around 70-90%. Sensitivity: 0.70-0.90 o (lower bound reflects non-initiation after prescribing; upper bound reflects high adherence) Specificity: 0.95-0.99 o (high specificity expected, as those without prescriptions are unlikely to be truly exposed) • In each Monte Carlo iteration, a single pair of sensitivity and specificity values will be drawn from the prespecified distributions and applied to both treatment groups, reflecting the assumption of non-differential misclassification. This approach avoids introducing artificial random differences in initiation of medication use between treatment arms while allowing uncertainty in the overall degree of misclassification to be propagated. [11,12]. These values will be used to probabilistically adjust the pooled hazard ratio for exposure misclassification using established bias-adjustment methods for dichotomous exposure classification. • Repeating this process across many iterations (e.g., 10,000) will generate a distribution of bias-adjusted hazard ratios. Final uncertainty will be represented by the percentile-based 95% confidence interval from the distribution of simulated bias-adjusted hazard ratios, which is derived from the empirical distribution of bias-adjusted point estimates across all Monte Carlo iterations

	and incorporates uncertainty from sampling variability, and exposure misclassification, rather than from confidence intervals calculated within individual iterations Although not verifiable, misclassification is assumed to be non-differential with respect to outcome. The limitations of this assumption will be acknowledged.
Assumptions	• Non-differential misclassification: exposure error is unrelated to the outcome. • Sensitivity and specificity are correctly specified and constant across individuals, over treatment arms. • The primary outcome model is correctly specified.
What is Being Varied?	• The assumption of accurate exposure measurement via prescribing • Simulate variation in sensitivity and specificity to generate corrected exposure measurement. • Assess how misclassification could bias the estimated hazard ratio.
Why (Objective)	• Evaluate whether the findings are robust to exposure misclassification. • Determine whether plausible levels of misclassification could meaningfully alter the estimated treatment effect.
Strengths	• Explicitly incorporates uncertainty in exposure classification. • Produces a distribution of corrected effect estimates, not just a point estimate.
Limitations	• Requires accurate or defensible assumptions about Se and Sp. • Limited to non-differential misclassification.

8.6.6. Core Emulation Table – Estimation summary

Table 16. Core Emulation Table: Estimation Summary

Estimand 1 (primary estimand)

	Target Trial	**Target Trial Emulation**	**Comment**
Analysis Method	Cox Proportional Hazards model	IPT-weighted Cox model to estimate HR	IPTW used to emulate randomisation in observational data Trimming of PS represents a departure from the target trial but is considered best practice when using propensity score methods in emulation. By removing study participants in regions of non-overlap, the analysis is restricted to a population where treatment assignment

	Target Trial	Target Trial Emulation	Comment
			is comparable across groups. As a result, the estimated effect no longer applies to the entire population but to this more comparable subset. If some study participants have an extremely low probability of receiving one of the treatments, valid causal contrasts cannot be identified for them. Without trimming, effect estimates in these regions rely on unsupported extrapolation, making the results unstable and potentially biased.
Missing Data Assumptions and Methods to Handle	Assumes noninformative censoring given treatment group and not experiencing the event up to the time of censoring; censored participants contribute partial information under Cox models	Noninformative given treatment group, survival up to the time of censoring and model covariates	
Statistical Model Assumptions	Proportional hazards Non-informative censoring Correct specification of the Cox model (functional form and covariates)	Same, and in addition: • **IPTW Assumptions**: no unmeasured confounding, positivity, correct model specification, consistency	To correctly model the propensity score, the model should include all risk factors of the outcome. However, this assumption is difficult to test in practice and has been addressed in this study by expert opinion-based risk factor list, confirmed by review of previous studies on pneumonia risk in adolescents, and previous studies on these medications and pneumonia in adults. Positivity assumption ensures there are comparable individuals for different values of propensity scores (or combination of risk factor values).

	Target Trial	Target Trial Emulation	Comment
Sensitivity Analyses	Sensitivity analysis under the CNAR assumption will be carried out.	Sensitivity analyses with IPCW to determine whether results are sensitive to alternative assumptions about censoring, i.e. censoring at random conditional on additional baseline and time-varying covariates. Best/worst case scenario analyses for exposure misclassification	

Estimand 2

	Target Trial	Target Trial Emulation	Comment
Analysis Method	AFT model followed by estimation of restricted mean survival time	IPT-weighted AFT followed by estimation of restricted mean survival time	IPTW used to emulate randomisation in observational data. Trimming of PS represents a departure from the target trial but is considered best practice when using propensity score methods in emulation. By removing study participants in regions of non-overlap, the analysis is restricted to a population where treatment assignment is comparable across groups. As a result, the estimated effect no longer applies to the entire population but to this more comparable subset. If some study participants have an extremely low probability of receiving one of the treatments, valid causal contrasts cannot be identified for them. Without trimming, effect estimates in these regions rely on unsupported

	Target Trial	Target Trial Emulation	Comment
			extrapolation, making the results unstable and potentially biased.
Missing Data Assumptions and Methods to Handle	Assumes noninformative censoring given treatment group and not experiencing the event up to the time of censoring; censored participants contribute partial information	Same	
Statistical Model Assumptions	Survival times follow Weibull distribution Non-informative censoring Log linear relationship between covariates and log linear survival time	Same, in addition **IPTW Assumptions**: no unmeasured confounding, positivity, correct model specification, consistency	To correctly model the likelihood of exposure, the model should include all risk factors of the outcome. However, this assumption is difficult to test in practice and has been addressed in this study by expert opinion-based risk factor list, confirmed by review of previous studies on pneumonia risk in adolescents, and previous studies on these medications and pneumonia in adults. Positivity assumption ensures there are comparable individuals for different values of propensity scores (or combination of risk factor values).
Sensitivity Analysis	None	None	

Estimand 3

	Target Trial	Target Trial Emulation	Comment
Analysis Method	Cox Proportional Hazards model	IPT-weighted Cox model to estimate HR	Cox model selected to reflect treatment policy estimand; IPTW used to emulate randomisation in observational data. Trimming of PS represents a departure from the target trial but is considered best practice when using propensity score methods in emulation. By removing study participants in regions of non-overlap, the analysis is restricted to a population where treatment assignment is comparable across groups. As a result, the estimated effect no longer applies to the entire population but to this more comparable subset. If some study participants have an extremely low probability of receiving one of the treatments, valid causal contrasts cannot be identified for them. Without trimming, effect estimates in these regions rely on unsupported extrapolation, making the results unstable and potentially biased.
Missing Data Assumptions and Methods to Handle	Assumes noninformative censoring; censored participants contribute partial information under Cox models	Same; administrative censoring used	
Statistical Model Assumptions	Proportional hazards Non-informative censoring	Same, in addition • **IPTW Assumptions**: no unmeasured confounding, positivity, correct model	To correctly model the likelihood of exposure, the model should include all risk factors of the outcome. However,

	Target Trial	Target Trial Emulation	Comment
	Correct specification of the Cox model (functional form and covariates)	specification, consistency No Unmeasured Confounding for Censoring	this assumption is difficult to test in practice and has been addressed in this study by expert opinion-based risk factor list, confirmed by review of previous studies on pneumonia risk in adolescents, and previous studies on these medications and pneumonia in adults. Positivity assumption ensures there are comparable individuals for different values of propensity scores (or combination of risk factor values).

8.7. *Data sources*

8.7.1. Data sources and Quality

Reason for selection / Rationale for selection and feasibility:

Finnish national registers and CPRD were selected as data sources for this study because they offer large, high-quality, population-based electronic health records with national coverage in Finland and the UK, respectively. Both sources provide the required data elements to operationalise the study design, including demographics, primary and secondary healthcare diagnoses, prescriptions and mortality data. Finnish national registers on dispensed prescriptions, primary and secondary healthcare contacts and causes of death are linkable through the National Hearth and Data Permit authority Findata, while CPRD offers linkage of written prescriptions to hospital and mortality records through NHS Digital. Both databases have previously been used in studying pneumonia incidence and risk factors as well as the utilization and outcomes of different asthma medications. They have been used in regulatory studies and are known to support the emulation of clinical trial eligibility criteria and endpoints. Their extensive follow-up time (median ~7 years for existing instance of Finnish registers and ~6–13 years for CPRD) makes them suitable for assessing the outcomes outcome. Data extraction and feasibility assessments confirm that the study variables are available with sufficient completeness and temporal coverage to support the research objectives.

Strengths of data sources:

Finnish registers cover the entire population of Finland (ca. 5.5M), and provide high completeness and reliability for critical variables such as date of birth, sex, specialized and primary healthcare admissions including diagnostic codes (ICD-10), and all dispensed prescriptions (ATC codes) and mortality including causes of death. Data for most registers are updated annually, for some of them continuously.

CPRD covers over 19 million patients in total, with 16.5 million current acceptable patients in Aurum and nearly 3 million in GOLD. The data are updated frequently (monthly for GOLD, quarterly for Aurum), and mortality, prescribing, and diagnosis information are available with high completeness. CPRD includes validated linkages to secondary care. Both databases support validated outcome definitions and have been widely used in pharmacoepidemiological studies.

Limitations of data sources (with potential impact on study results):

For both databases, dose information of ICS is not routinely available and as the pneumonia risk associated with ICS is dose-dependent this can potentially introduce bias to the results. However, the ICS component of study treatment is fixed, and add-on ICS treatments are handled with a treatment policy approach, reflecting the use of these medications in routine clinical settings. Further, the necessity of introducing additional ICS during the combination treatment can be considered as an association mediator. Information on possible pneumonia risk factors, which are household-related related risk factors (such as exposure to smoking, crowded housing, parental socioeconomic position) is missing, but we attempt to capture this with comorbidity proxies. Both databases miss information on asthma severity, which is captured by proxies (such as asthma-associated hospitalisations, use of add-on or additional rescue medications). For CPRD, cause of death is not available and therefore misclassification of outcome is possible. This is assessed by conducting an additional estimand in Finnish data (estimand 3), in which pneumonia is ascertained also from the causes of death register. For CPRD, month of birth is available for individuals aged ≤16 years and year of birth for 17-year-olds, which may slightly impact precision in age-based eligibility criteria.

Data Quality:

Table 17. Overall feasibility assessment summary for the Finnish registers and CPRD used in CS5 (Vilanterol/fluticasone furoate in the risk of pneumonia in adolescents with asthma)

RWD source	Sample size estimation from the hypothetical trial protocol	Feasibility assessment *(yes/yes, with limitations/no)*	Rationale for the feasibility assessment	Limitations identified during the feasibility assessment and categorisation	Description of potential impact of the identified limitations on the study results
CPRD	With an approximate estimated sample size of 26,750 individuals (based on a 1:1 ratio between treatment arms, with 13,375 participants in each), and considering that CPRD includes data from approximately 4.4 million inhabitants (as of 2014), the target cohort size is anticipated to be achievable. In the UK, asthma affects approximately 7.2 million individuals—about 8% of the population—with up to 5.4 million currently receiving any treatment. This translates to approximately 281,600 subjects. Teenager population in CPRD is 200,949, and the prevalence of asthma in UK teenagers is 15.2%, this translates in 30,544 astmathic teenagers in CPRD. The target sample size is anticipated to be reached.	Yes	Elements with high criticality are available and fairly reliable. Data recency of 3 months before extraction, reasonably enough for the research question. Sample size is achievable.	1.Potentially major: Hospitalisation data is not available for the core data source. 2.Potentially major: Not registered date of death. 3.Minor: Dispensing is not available, only prescription. 4.Minor: Diagnostic codes are available for 86% subjects attending emergency room.	1.The DEAP is able to perform data augmentation (linkage) to retrieve hospital admission and discharge diagnoses to detect the outcomes of this case-study. 2.For exact date of death or the cause of death data augmentation (linkage) is needed to the ONS death registration data. 3.As this database only has prescription data, it is unknown if patients took the prescription, and so, if they discontinued it. However, treatment duration is available, from which this data may be estimated. 4.Diagnostic codes are reported to be available for 86% of subjects in the emergency room; however, the missing cases we expect to capture them from hospitalisation records or primary care records, since the severity of this disease may justify an admission and/or the follow-up with the GP, or change of baseline treatment.

RWD source	Sample size estimation from the hypothetical trial protocol	Feasibility assessment *(yes/yes, with limitations/no)*	Rationale for the feasibility assessment	Limitations identified during the feasibility assessment and categorisation	Description of potential impact of the identified limitations on the study results
Finnish registers	With an approximate estimated sample size of 26,750 individuals (based on a 1:1 ratio between treatment arms, with 13,375 participants in each), and considering that Finland has a population exceeding 5 million (380,000 individuals aged 12-17y, 10.5% with asthma). Despite there is up to 18,293 users of vilanterol-fluticasone furoate among the 233,261 patients with chronic asthma or similar chronic obstructive pulmonary diseases as of 2021, there is no specific data available for teenage users. Since the number of teenage users is expected to be smaller than the target sample size, we anticipate that reaching the desired sample may not be feasible.	Yes, with limitations on sample size acquisition	Elements with high criticality are available and fairly reliable. Data recency is variable depending on the data sets used, but for the current case, a few months are reasonably enough for the research question. The time elapsed from when a user requests the data to when they actually receive it is 4-12 months. **Sample size might be difficult to be reached**.	1.Potentially major: limited sample size. 2.Minor: No in-hospital drug use available. 3.Minor: Duration of hospitalisation is not readily available. 4.Minor: Exacerbations inhospital are not available. 5.Minor: Duration of treatment and end of treatment are not directly available.	1. Limited sample size in Finnish registers might lead to underpowered analyses for this population. This can be mitigated by meta-analysing the results together with CPRD. 2.Duration of hospitalisation can be calculated from the admission and discharge dates. 3.Inhospital exacerbations can be inferred from admission, discharge and primary care diagnoses that are readily available. 4.End of treatment episodes may be derived based on dispensing date and dispensed amount.

Table 18. Metadata about data sources and software

	Data 1 (Finnish registers)	Data 2 (CPRD)
Data Source(s):	Finnish national registers	CPRD Aurum
Study Period:	1.1.2017–31.12.2023	1.1.2016–16.09.2024
Eligible Cohort Entry Period:	1.1.2017–31.12.2023	1.1.2016–15.9.2024
Data Version (or date of last update):	June 2024	CPRD Aurum: Sepetember 2025
Data sampling/extraction criteria:	Persons with asthma diagnosis aged 12-17, receiving at least one prescription for vilanterol/fluticasone furoate or another single device ICS+LABA combination ≥1 year lookback and two years follow-up	Persons with asthma diagnosis aged 12-17, receiving at least one prescription for vilanterol/fluticasone furoate or another single device ICS+LABA combination ≥1 year lookback and two years follow-up
Type(s) of data:	Primary and secondary care admission data dispensed prescriptions, causes of death, demographics	Primary care EHR, linked secondary care data (HES), prescriptions, lab values, demographics, outcomes
Data linkage:	Deterministic linkage with unique personal identification numbers	Yes: deterministic linkage with HES, ONS mortality, NCRAS, etc. (linkage via NHS number, DOB, postcode, sex)
Conversion to CDM*:	Yes: OMOP and CONCEPTION	Yes: OMOP CDM, also CONCEPTION CDM
Software for data management:	R and Python, analyses in audited remote use environment	SAS 9.4 and R, analyses in secured virtual desktop environment

8.8. *Data Management*

The study was conducted in a distributed manner using the UMCU, ARS Toscana and VAC4EU tools, procedures, and pipeline. Figure 2 specifies the data sets (D) and transformation processes (T), programming follows this pipeline, with involvement of different types of experts.

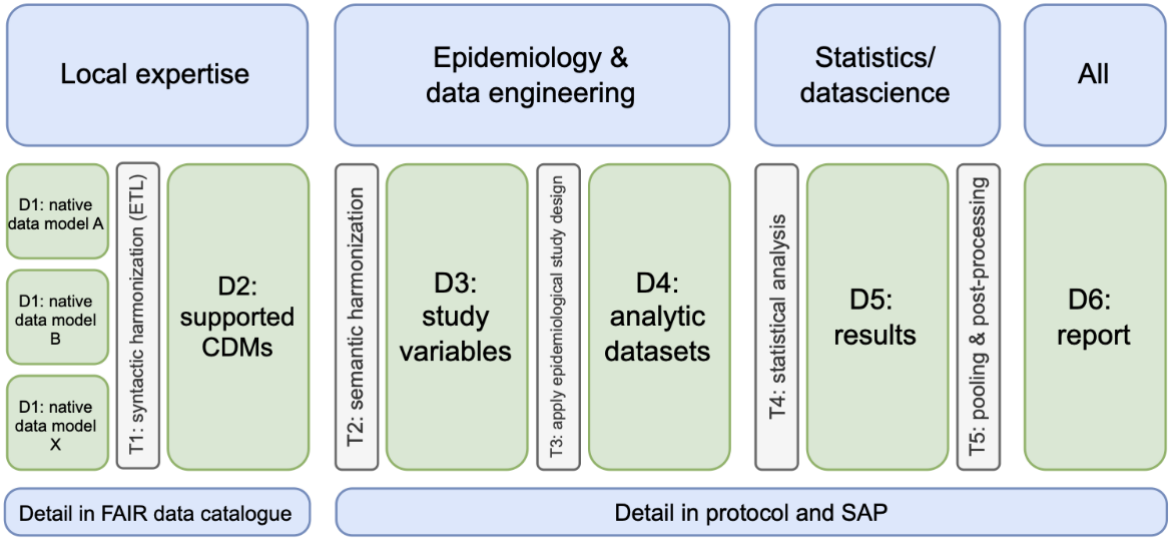


Figure 2. Data Management from the data transformation perspective

D1: Original data can be in any native format

The RWD-RWE pipeline used by VAC4EU starts with data banks that are controlled by the Data Expert and Access Partner (DEAP) and can be in any format. Data always stays local and never leaves the secure environments of the DEAPs. The ETL (extract, transform, load, see below for more details under 'T1') design is shared in a searchable FAIR VAC4EU catalogue. The VAC4EU FAIR Molgenis data catalogue is a meta-data management tool designed to contain searchable meta-data describing organisations that can provide access to specific data sources.

T1: Syntactic harmonisation (ETL)

T1: Syntactic harmonisation is conducted through an extraction, transformation, and loading (ETL) process of native data into the ConcePTION common data model (CDM) (see section 'D2: Common data model'). To harmonise the structure of the data sets stored and maintained by each data partner, a shared syntactic foundation is used. The ETL process has various structured steps as described by Thurin et al (2021):

- DEAPs are asked to share the data dictionaries of their data banks (selected tables and variable names/structure)
- Metadata (descriptive data about the data sources and databanks) & data dictionaries, are uploaded in FAIR data catalogue (Molgenis).

D2: Common data model

For this project, the CDM (D2) is the ConcePTION common data model. The CDM version v2.2 was used, and it is available as an open-source CDM. In this CDM, data are represented in a common structure, but the values of the data remain in their original language (e.g. codes will have either ICD9/10/ICPC/SNOMED or MEDCODEID values).

T2: Semantic harmonisation

During the T2 step, many data transformations occur related to the completion of missing features in the data. Based on the relevant diagnostic medical codes and keywords, as well as other relevant concepts (e.g., medications), one or more phenotype algorithms are constructed (typically one sensitive, or broad, algorithm and one specific, or narrow, algorithm) to operationalise the identification and measurement of each event. In this step we conduct time anchoring (observation periods, look back periods), clean the data such as the dose of vaccines, sort on record level, aggregate across multiple records, and combine concepts for implantation of algorithms, and rule-based creation of study variables.

In this phase of the creation of study variables, semantic mapping is conducted. This semantic mapping across different vocabularies is conducted as part of the R-study script using different functionalities. To reconcile differences between different terminologies and native data availability, machine-readable code lists are used that comprise the terminologies that are used in the network (e.g. ICD-9, ICD10, SNOMED, ICPC and DEAP specific adaptations). This is combined with the BRIDGE metadata file that defines risk windows, look-back periods, and algorithms for each study variable (65,66).

D3: Study variables

D3 datasets are interim data sets with information on study variables for each study participant, the unit may be a person, a medicine, or episode of time. The design of these datasets is described in codebooks. Examples of D3 datasets are the outputs of the ConcePTION pregnancy algorithm, and outputs of functions that define smoking. Multiple functions/packages exist within the VAC4EU, for different study variables.

T3: Application of epidemiological design

In the T3 step epidemiological designs were applied such as sampling, matching (on specific variables and/or propensity scores), and selection based on inclusion and exclusion criteria using the study variables in the D3 datasets. The designs were implemented for the various study objectives using R-scripts, and these may use the existing functions (R-cran) or functions that have been developed in the VAC4EU community (e.g. matching).

D4: Analytical data set

D4 is an analytical dataset, and multiple D4 data sets may be produced based on the objectives of the study. The format is described initially in a code book for communication between programmers and statisticians.

T4: Statistical analysis

This step in the data transformation pipeline will produce statistical estimates such as descriptives (counts, percentages), distributions (mean, percentiles), rates (prevalence, incidence), regression coefficients, or other relevant estimates. This will be conducted using R.

D5: Results

D5 is the set of estimates, tables or aggregate data that is transferred from the DEAPs to the Digital Research Environment (DRE). The aggregated results produced by these scripts at the DEAP's site will be uploaded to the UMCU DRE for post-processing, pooling and visualisation (Figure 2). The DRE is a cloud-based, globally available research environment where data are stored and organised securely and where researchers can collaborate. The DRE is made available through UMCU. The DRE applies double authentication where researchers can collaborate using data that are stored and organised securely [ref]. UMCU is responsible for data processing and data security.

All researchers who need access to the DRE will be granted access to study-specific secure workspaces by UMCU. Access to the workspaces will be possible only after double authentication using an identification code and password together with the user's mobile phone for authentication.

Uploading files will be possible for all researchers with access to the workspace within the DRE. Downloading of files will be possible only after requesting and receiving permission from a workspace member with an "owner" role, who will be a UMCU team member.

T5: Post-processing/pooling

In this step, the result from different DEAPs is pooled and converted into tables and figures for reporting.

8.9. *Quality Control*

All key study documents such as the hypothetical trial protocol, target trial emulation protocol and study reports will undergo senior scientific and editorial review.

Data quality

For all data sources and for each data instance we will conduct *INSIGHT* level 1-2 quality checks, detailed statistical analysis plans for the indicators are available on the public repositories:

- https://github.com/UMC-Utrecht-RWE/INSIGHT-Level1 Hoxhaj, V. (2023). UMC-Utrecht-RWE/INSIGHT-Level1: https://doi.org/10.5281/zenodo.10035167
- https://github.com/UMC-Utrecht-RWE/INSIGHT-Level2 Hoxhaj, V., & van den Bor, R. (2023). UMC-Utrecht-RWE/INSIGHT-Level2: https://doi.org/10.5281/zenodo.10035169

Briefly, level 1 verifies Data Completeness and level 2 Data Consistency.

Level 1 – Data Completeness

The purpose of the level 1 check is to verify the completeness of the ETL process and the data in the variables. Examples of tests are:

- Presence of variables in each of the CDM tables in D2
- Checks for misspellings and letter case in variable names in each of the CDM tables
- Verification of vocabularies
- Check date formats
- Check conventions of values
- Missing data analysis
- Frequency tables for categorical variables

Level 2 – Data Consistency

Real data is not random but follows certain logical constraints that reflect rules governing real-world situations. Examples of indicators generated by level 2 checks are:

- Event dates before date of birth
- Event dates after date of death
- Event dates out of observation periods
- Subjects having an observation but not present in the PERSONS table

- Observations associated with a visit id and occurred before/after the visit start/end date
- Subjects younger than 12 years old reported as parents
- Age at the observation period older than 115 y old Data

Code Quality

These coding practices define how the TARGET programming team collaborates to write clean, reliable, and reproducible code for the VAC4EU Real-World Evidence (RWE) Analytical Pipeline. They aim to ensure clarity, consistency, and maintainability across all case studies within the project.

Coding conventions

To ensure clarity, consistency, and maintainability across the project, the following conventions will be applied to all codebases within the project:

- Consistent style: Code follows a consistent and readable style (see the tidyverse style guide for R).
- Meaningful names: Use clear, descriptive names for variables, functions, and files to convey their purpose.
- Modular code: Break down code into small, reusable functions where possible.
- No hardcoded paths: Use configuration files or relative paths to ensure portability.

Following these conventions makes the code easier to understand, test, and reuse across case studies and teams.

Documenting Code

Code documentation is used to promote good coding practices and ensure our work is understandable, maintainable, and reproducible. To achieve this, we will:

- Use descriptive comments that explain the purpose and rationale behind code sections, focusing on why something is done, not just what.
- Clearly document function inputs, outputs, and side effects, using standardized formats (e.g., roxygen2 in R) where appropriate and supported.
- Write meaningful variable and function names to make the code as self-explanatory as possible.

Version *Control*

We use Git and GitHub to manage version control. These tools support good coding practices by enabling collaboration, tracking changes, accessing a project's history, and ensuring code quality through review and documentation.

A dedicated GitHub organisation has been created for the project (https://github.com/target-roc19). Each case study is managed in its own repository within this organisation. Repositories are structured consistently across case studies, to reinforce modularity. Access to repositories is controlled through teams.

During development, all repositories remain private to ensure confidentiality. Once the project is finalised, relevant repositories will be made public and assigned a digital object identifier (DOI) via Zenodo to support transparency, reproducibility, and reuse by the wider research community.

To maintain code quality and clarity, we follow the git and GitHub guidelines below.

- Always use pull requests (PRs): never push directly to the main branch.
- Open an issue before creating a new branch. Ideally, one PR resolves one issue to keep changes focused and reviewable.
- Every PR must be reviewed by at least one other person before merging.
- The PR author merges the PR after it has been reviewed and approved.
- Write clear, descriptive commit messages.
- Write informative PR descriptions, including:
    - A concise title
    - Links to related issues
    - A summary of the changes

Continuous Integration

Continuous Integration (CI) is set up to automatically check code quality and run tests whenever changes are pushed to the repository or submitted through a pull request (PR). The CI workflow ensures that the package adheres to predefined style guidelines and that all automated tests pass before changes are merged.

Coding Template

Every case study follows the general coding template used across all code in the TARGET project. The folder structure is organised as follows:

case-study-template

|____data

| |____D2_cdm

| |____D3_study_variables

| |____D4_analytic_datasets

| |____D5_results

| |____D6_report

|____docs

|____logs

|____run

|____tests

|____transformations

| |____T2_semantic_harmonization

| |____T3_study_design

| |____T4_statistical_analysis

| |____T5_processing_results

|____CHANGELOG.md

|____LICENSE

|____README.md

Project Data Structure and Storage

The data folder follows the Real-World Evidence pipeline structure. Data conforming to the common data model is stored in the D2_cdm folder.

Results from transformations T2, T3, T4, and T5 are saved in the respective folders:

- D3_study_variables
- D4_analytic_datasets
- D5_results
- D6_report

Each dataset is associated with a codebook, explained in more detail below.

All data remain securely stored on the Data Expert and Access Partners (DEAPs) servers and are never transferred externally. For testing purposes, dummy datasets are created. These fall into two categories:

- Unit test data: Small, predefined input and output pairs used to test individual transformation steps. These are stored in the tests folder, not in data, and can support automated testing.
- Pipeline test data: Larger, more complex dummy datasets used to test whether the full pipeline runs as expected. These may be included in the repository only if they remain below GitHub's 100 MiB file size limit and will otherwise be shared via SharePoint.

Logging System

When the pipeline is executed, log files are saved in the logs folder. These logs are especially helpful when running the code in the DEAPs environment, as they help trace and diagnose potential errors. We recommend using the logger R package to handle logging throughout the pipeline. A sample logging setup can be found in the logger.R script located at the root of the project directory.

Executing the Analytical Pipeline

The run folder contains scripts used to execute each transformation step in the pipeline.

- A central script, run_pipeline.R, orchestrates the full pipeline from start to finish.
- Subscripts (e.g., run_T2.R or similar) are available to run individual transformation steps separately.

Typically, the run_pipeline.R script is the main entry point used by a DEAP to execute the full pipeline. Before running it in the DEAP environment, the pipeline may need to be adapted to local settings. This can be done using a configuration file that defines variables required to tailor the pipeline to a specific DEAP. Please note that configuration files should not include sensitive information.

Such a file might include variables like:

- The name of the DEAP
- The path to the local data instance
- The path to any required external resources

Testing and Quality Assurance

The tests folder contains scripts to test the analytical pipeline. Tests will be used to ensure code behaves as expected and remains stable over time. By systematically checking inputs, outputs, and edge cases, tests help catch errors early and make future changes safer. We use the testthat R package to structure and run unit tests.

Continuous integration (CI) is used to automate testing. With CI, tests are automatically run each time code is pushed to the repository (e.g., via GitHub Actions). This helps identify issues immediately, ensures that new changes do not break existing functionality, and supports better collaboration by enforcing consistent code quality across contributors.

Modular Data Transformation Workflow

The transformations folder follows the Real-World Evidence pipeline structure. It contains the source code for all transformation steps, which is typically written in R. Each subfolder corresponds to a specific step in the pipeline (e.g., T2_semantic_harmonization, T3_study_design, T4_statistical_analysis, T5_processing_results) and includes the relevant scripts and helper functions for that step.

During the T2 step, a database is usually created (e.g., using DuckDB). This database can be queried using SQL, and it is recommended that all SQL queries be saved as clearly named, standalone SQL script files to ensure readability and reusability.

The purpose of the transformations folder is to structure and modularise the processing logic, making it easier to maintain, test, and reuse across different case studies. By organising code by transformation step, teams can work in parallel, increasing efficiency.

Changelog

A changelog will be kept for all notable changes in the project. Changelogs help track the evolution of the project over time, making it easier for collaborators to understand what has changed between versions. We follow the structure and best practices outlined in Keep a Changelog.

Codebooks

Before developing code, codebooks are created to describe each dataset (D) within the pipeline. A codebook is a comprehensive document that outlines the structure, contents, and metadata of a dataset. It serves as a detailed reference guide for anyone working with the data and plays a crucial role in guiding the development of the analytical pipeline by clearly defining both the inputs and expected outputs.

All codebooks are summarized in a central index file, which provides a high-level overview of the pipeline's structure. For each codebook, the index file includes:

- A brief description of its purpose,
- A list of the scripts used to generate the corresponding dataset,
- A description of the input datasets and input parameters required.

The datasets D2, D3, D4, and D5 are typically subdivided into multiple smaller transformation steps, each detailed within their respective codebooks. These smaller transformation steps ensure that each part of the pipeline is clearly scoped and well-documented.

In addition to supporting development, codebooks help ensure quality control by making transformation logic transparent and verifiable, and they enhance reproducibility by documenting exactly how data is structured and used throughout the analytical pipeline.

Deployment

The analytical pipeline is delivered to DEAPs as a GitHub release, tagged with a version number. Versioning follows the format: vYYYYMMDD.XX, where the date indicates the release date and XX denotes the sub-version or revision number.

Any deployment issues can be reported via the GitHub repository using the issues feature, where the programming team responsible for the R code will collaborate with the local DEAP to resolve them as needed.

Reproducibility

It is recommended to locally use the renv R package to maintain the R version and version of packages for reproducibility purposes.

At this time, however, using renv reliably across different systems and environments remains challenging. For this reason, we currently recommend its use only in local development setups.

We are actively monitoring developments in the R ecosystem related to cross-platform reproducibility. As soon as a more stable and portable solution becomes available, we will revisit this guidance and promote broader adoption.

Licensing

The code will be made available under an open source license.

README Guidelines

Each case study repository includes a README that covers the following points:

- Project Overview: brief summary of the study goals and key research questions.
- Background: context and rationale for the study.
- Repository Structure: Outline of main folders and their contents.
- Data Overview: Description of data sources, formats, and data privacy considerations.
- How to Run: Instructions for running the pipeline and key scripts, plus where outputs are saved.
- Testing: How to run tests to verify code functionality.
- Contributing: Guidelines for code contributions and issue tracking.
- License: Information about the code license.
- Contact: Who to reach out to for help or questions.

9. Deviations from Protocol

One of the preplanned propensity score covariates, ICS strength at baseline, was omitted in both CPRD and FinReg because this information could not be reliably extracted at the time of report submission. Given that Nordic product numbers are recorded for most dispensings in FinReg and should permit identification of ICS strength, this omission appears to result from study implementation challenges rather than limitations of the underlying data source.

However, information on other proxies of asthma severity are included as propensity score covariates (for example add-on treatment use of LTRA, biologicals, SAMA, antibiotics as a proxy for bacterial infections, asthma exacerbations and use of oral corticosteroids).

We also changed the operationalisation of asthma exacerbation (Section 8.4.4., Table 11) to include all hospitalisations, not only overnight hospitalisations as this is considered to be a better proxy for severe exacerbations particularly in CPRD because it would capture also emergency visits that do not last overnight. However, in FinReg this revised definition likely overestimates the exacerbations as annual control visits to asthma policlinic in specialised healthcare are not distinguishable from emergency visits with the currently available data. The impact of this is discussed further in the limitations section.

Several planned sensitivity and supplementary estimand analyses could not be completed because of the limited sample size, low number of pneumonia events, and sparse censoring patterns observed during follow-up. Results of the sensitivity analysis for nondifferential exposure misclassification could not be calculated for UK CPRD due to masking of small event counts. Estimand 2 could not be computed in CPRD because the models did not converge due to small number of pneumonia events. Estimand 3 was not calculated because its censoring distribution was identical to that of the primary estimand, with no additional pneumonia cases identified from the causes-of-death register, as no censoring occured due to death for Estimand 1. The IPC-weighted sensitivity analyses could not be conducted in FinReg because the analysis did not converge due to small number of nonadministrative censoring events.

Finally, in the approved protocol we had misspecified the tipping point analyses (Table 14) to assess the impact of missing data due to nonadministrative censoring and discontinuation/switching. In this study report, the description has been revised in Table 14 to refer only to non-administratively censored individuals, consistent with the primary estimand and the corresponding analysis approach.

10. Results

10.1. *Study Population*

Figure 3 shows the number of individuals included in the study from the two databases. We identified 6073 people in the Finnish registers and 26506 people in UK CPRD aged 12-17 years with asthma diagnosis and on ICS treatment the previous year. After applying the prespecified exclusion criteria, we identified 2699 and 8666 eligible study participants initiating vilanterol-fluticasone furoate combination or other single-device inhaled corticosteroid-long-acting beta-2 adrenoceptor agonist combination in the Finnish registers and UK CPRD, respectively. The most common reason for exclusion was prevalent use of either V+FF or other ICS-LABA combination and the number of participants was significantly smaller than the target sample size of 26,750 persons in both treatment groups.

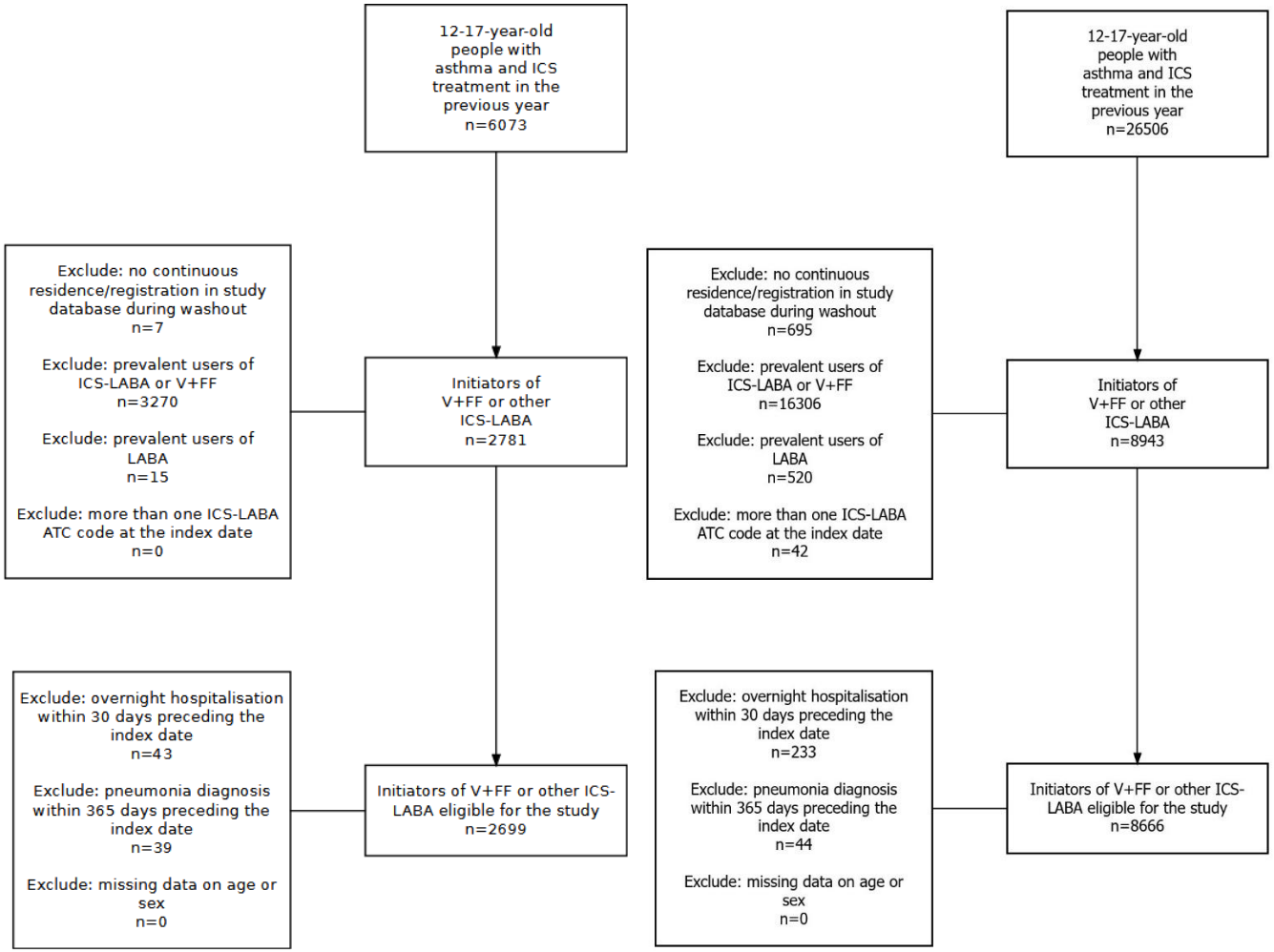


Figure 3. Flowcharts of participant exclusion in Finnish registers (on the left) and UK Clinical Practice Research Datalink (on the right).

10.2. *Patient Characteristics*

Table 19 and Table 20 show the baseline covariates of individuals initiating V+FF and other single-device ICS+LABA combination treatments before and after weighting in UK CPRD and in Finland. Before weighting, differences were seen in several baseline covariates between patients initiating V+FF compared with patients initiating other ICS+LABA. Patients initiating V+FF were median 1 year older than patients initiating other ICS+LABA combinations in UK CPRD (median age 15 (interquartile range (IQR) 13-16) vs 14 (IQR 13-16); aSD 0.26) while of comparable age in Finland (median age 14 (IQR 13-16) vs 14 (IQR 13-16); aSD 0.167). Use of antibiotics was more common among other ICS+LABA initiators in both databases than among those initiating V+FF. In UK CPRD, influenza vaccinations were more common among V+FF initiators, whereas use of oral corticosteroids and leukotriene receptor antagonists was more common among initiators of other ICS+LABA. In both UK CPRD and FinReg, asthma exacerbations were less common in the other ICS+LABA group. In Finland, diabetes was more frequent among V+FF initiators and hospital days and outpatient visits were more frequent among other ICS+LABA users. Other conditions affecting swallowing ability and pneumonia risk were rare among all initiators in both databases. In CPRD, the initiations of other ICS+LABA were more evenly distributed across the study years, apart from one peak of 20.5% in 2023. There was more fluctuation in the V+FF initiations across the years. In Finland, the distribution of other ICS+LABA initiations and V+FF initiations across the study years was comparable, and highest in 2020, 2021 and 2023 for V+FF initiations. Both, V+FF and ICS+LABA initiators most frequently entered in autumn in CPRD while in spring and autumn in Finnish registers.

After weighting, the baseline covariates were balanced between the two treatment groups in both databases. In addition, in FinReg trimming was applied to remove 2 V+FF initiators and 10 other ICS+LABA initiators from the nonoverlapping parts of the PS distribution.

Table 19. Standardised mean differences for baseline covariates before and after weighting (stabilized IPT weights without truncation) in UK CPRD

	Before weighting				After weighting			
Characteristic	Overall (n=8666)	V+FF (n = 617)	Other ICS+ LABA (n = 8049)	aSD*	Overall (n=8663.5)	V+FF (n = 614.8)	Other ICS+ LABA (n =8048.7)	aSD*
Demographics								
Age at index, median (IQR)	14 (13-16)	15 (13-16)	14 (13-16)	0.26	14 (13-16)	14 (13-16)	14 (13-16)	0.041
Sex, n (%)								
Women/Girls	4536 (52.3%)	337 (54.6%)	4199 (52.2%)	0.049	4537.7 (52.4%)	324.3 (52.8%)	4213.3 (52.3%)	0.008
Men/Boys	4130 (47.7%)	280 (45.4%)	3850 (47.8%)	0.049	4125.8 (47.6%)	290.4 (47.2%)	3835.4 (47.7%)	0.008
Other		0 (NR)	0 (NR)	0		0 (NR)	0 (NR)	0
Calendar year, n (%)								
2016	856 (9.9 %)	29 (4.7%)	827 (10.3%)	0.213	849.2 (9.8%)	54.1 (8.8%)	795.1 (9.9%)	0.037
2017	940 (10.8%)	40 (6.5%)	900 (11.2%)	0.166	934.8 (10.8%)	61.8 (10%)	873 (10.8%)	0.026
2018	900 (10.4%)	57 (9.2%)	843 (10.5%)	0.041	900.7 (10.4%)	64.7 (10.5%)	836 (10.4%)	0.004
2019	1134 (13.1%)	130 (21.1%)	1004 (12.5%)	0.232	1128.3 (13%)	76 (12.4%)	1052.3 (13.1%)	0.021
2020	927 (10.7%)	76 (12.3%)	851 (10.6%)	0.055	934.8 (10.8%)	73.3 (11.9%)	861.6 (10.7%)	0.038
2021	936 (10.8%)	73 (11.8%)	863 (10.7%)	0.035	938.6 (10.8%)	69.1 (11.2%)	869.5 (10.8%)	0.014

	Before weighting				After weighting			
2022	1222 (14.1%)	112 (18.2%)	1110 (13.8%)	0.119	1218.4 (14.1%)	83.6 (13.6%)	1134.8 (14.1%)	0.014
2023	1751 (20.2%)	100 (16.2%)	1651 (20.5%)	0.111	1758.7 (20.3%)	132.2 (21.5%)	1626.4 (20.2%)	0.032
Season, n(%)								
winter	2290 (26.4%)	164 (26.6%)	2126 (26.4%)	0.004	2288.8 (26.4%)	161.7 (26.3%)	2127.1 (26.4%)	0.003
spring	1978 (22.8%)	128 (20.7%)	1850 (23%)	0.054	1988.2 (22.9%)	150.7 (24.5%)	1837.6 (22.8%)	0.04
summer	1888 (21.8%)	141 (22.9%)	1747 (21.7%)	0.028	1869.7 (21.6%)	117.4 (19.1%)	1752.3 (21.8%)	0.066
autumn	2510 (29%)	184 (29.8%)	2326 (28.9%)	0.02	2516.8 (29.1%)	184.9 (30.1%)	2331.8 (29%)	0.024
Comorbidities, n(%)								
Diabetes	26 (0.3%)	5 (0.8%)	21 (0.3%)	0.075	26.1 (0.3%)	2 (0.3%)	24.2 (0.3%)	0.003
Rheumatological diseases	209 (2.4%)	16 (2.6%)	193 (2.4%)	0.013	207.1 (2.4%)	13.1 (2.1%)	194 (2.4%)	0.019
Malignancies	63 (0.7%)	6 (1%)	57 (0.7%)	0.029	64.3 (0.7%)	5.6 (0.9%)	58.7 (0.7%)	0.019
Cardiovascular diseases	258 (3%)	24 (3.9%)	234 (2.9%)	0.054	258.8 (3%)	18.9 (3.1%)	239.9 (3%)	0.005
Intellectual disability	60 (0.7%)	<5 (NR)	NR		60.4 (0.7%)	<5 (NR)	NR	
Congenital malformations	5 (0.1%)	0 (NR)	5 (0.1%)	0.035	4.6 (0.1%)	0 (NR)	4.6 (0.1%)	0.034
Psychotropic drugs	404 (4.7%)	31 (5%)	373 (4.6%)	0.018	403.9 (4.7%)	28.5 (4.6%)	375.4 (4.7%)	0.001
Asthma exacerbations, n (%)								
0	7467 (86.2%)	514 (83.3%)	6953 (86.4%)	0.086	7468.1 (86.2%)	532.4 (86.6%)	6935.7 (86.2%)	0.013

	Before weighting				After weighting			
1-2	477 (5.5%)	38 (6.2%)	439 (5.5%)	0.03	480.3 (5.5%)	36.9 (6%)	443.4 (5.5%)	0.022
>=3	722 (8.3%)	65 (10.5%)	657 (8.2%)	0.082	715.1 (8.3%)	45.4 (7.4%)	669.7 (8.3%)	0.035
Healthcare use during washout, n (%)								
Number of hospital days, n (%)								
0	7929 (91.5%)	555 (90%)	7374 (91.6%)	0.057	7929.6 (91.5%)	565.3 (92%)	7364.3 (91.5%)	0.017
1-2	499 (5.8%)	40 (6.5%)	459 (5.7%)	0.033	495.8 (5.7%)	32.4 (5.3%)	463.3 (5.8%)	0.021
>=3	238 (2.7%)	22 (3.6%)	216 (2.7%)	0.051	238.2 (2.7%)	17 (2.8%)	221.1 (2.7%)	0.001
Number of outpatient visits, n (%)								
0-5	1256 (14.5%)	102 (16.5%)	1154 (14.3%)	0.061	1252.9 (14.5%)	86.4 (14.1%)	1166.5 (14.5%)	0.013
6-12	3277 (37.8%)	248 (40.2%)	3029 (37.6%)	0.053	3273.1 (37.8%)	229.4 (37.3%)	3043.7 (37.8%)	0.01
13-24	3026 (34.9%)	201 (32.6%)	2825 (35.1%)	0.053	3028.6 (35%)	218.1 (35.5%)	2810.5 (34.9%)	0.012
>=25	1107 (12.8%)	66 (10.7%)	1041 (12.9%)	0.069	1108.9 (12.8%)	80.8 (13.1%)	1028.1 (12.8%)	0.011
Medication use during washout, n (%)								
Oral corticosteroids	2530 (29.2%)	143 (23.2%)	2387 (29.7%)	0.147	2531.8 (29.2%)	181.7 (29.6%)	2350.1 (29.2%)	0.008
Biologicals	<5 (NR)	<5 (NR)	<5 (NR)		<5 (NR)	<5 (NR)	<5 (NR)	
Short-acting beta2-agonists (SABA)	8465 (97.7%)	602 (97.6%)	7863 (97.7%)	0.008	8463.2 (97.7%)	601 (97.8%)	7862.2 (97.7%)	0.005

	Before weighting				After weighting			
Short-acting muscarinic receptor antagonist (SAMA)	40 (0.5%)	<5 (NR)	NR		39.5 (0.5%)	<5 (NR)	NR	
Leukotriene receptor antagonists	2065 (23.8%)	122 (19.8%)	1943 (24.1%)	0.106	2059.4 (23.8%)	142 (23.1%)	1917.4 (23.8%)	0.017
Antibiotic use	2989 (34.5%)	185 (30%)	2804 (34.8%)	0.104	2979.4 (34.4%)	203.4 (33.1%)	2776 (34.5%)	0.03
Pneumococcal vaccination	6 (0.1%)	0 (NR)	6 (0.1%)	0.039	5.6 (0.1%)	0 (NR)	5.6 (0.1%)	0.037
Influenza vaccination	667 (7.7%)	69 (11.2%)	598 (7.4%)	0.129	664.7 (7.7%)	45.6 (7.4%)	619.1 (7.7%)	0.011

For all comorbidities and co-medications, absence of a record is considered absence of the corresponding comorbidity/co-medication.

Values are presented without imputation.

NR = not reportable

IQR = interquartile range

*For continuous variables aSD was calculated as the absolute difference in group means divided by the pooled standard deviation. For categorical variables, each level was treated as a binary indicator and the aSD is calculated as the absolute difference in proportions divided by the standard deviation of the difference of the two proportions; consequently for categorical covariates aSD is reported per level.

Table 20. Standardised mean differences for baseline covariates before and after trimming and weighting (stabilized IPT weights) in Finland

	Before trimming and weighting				After trimming and weighting			
Characteristic	Overall (n=2699)	V+FF (n = 600)	Other ICS+ LABA (n = 2099)	aSD*	Overall (n=2677.3)	After weighting: V+FF (weighted n = 590)	After weighting: Other ICS+LABA (weighted n = 2087.3)	aSD*
Demographics								
Age at index, median (IQR)	14 (13-16)	14 (13-16)	14 (13-16)	0.167	14 (13-16)	14 (13-16)	14 (13-16)	0.015
Sex, n (%)								
Women/Girls	1403 (52.0%)	292 (48.7%)	1111 (52.9%)	0.085	1392.2 (52.0	307.8 (52.2%)	1084.4 (52%)	0.004
Men/Boys	1296 (48.1%)	308 (51.3%)	988 (47.1%)	0.085	1285.1 (48.0%)	282.2 (47.8%)	1002.9 (48%)	0.004
Other		0 (NR)	0 (NR)	0		0 (NR)	0 (NR)	0
Calendar year, n (%)								
2017	373 (13.8%)	68 (11.3 %)	305 (14.5%)	0.095	370.2 (13.8%)	80.2 (13.6%)	290 (13.9%)	0.009
2018	380 (14.1%)	74 (12.3%)	306 (14.6%)	0.066	380.2 (14.2%)	84.8 (14.4%)	295.4 (14.2%)	0.006
2019	444 (16.5%)	89 (14.8%)	355 (16.9%)	0.057	437.9 (16.4%)	94.8 (16.1%)	343.1 (16.4%)	0.01
2020	400 (14.8%)	101 (16.8%)	299 (14.2%)	0.071	397.3 (14.8%)	87.6 (14.8%)	309.7 (14.8%)	0
2021	384 (14.2%)	103 (17.2%)	281 (13.4%)	0.105	380.3 (14.2%)	85.2 (14.4%)	295.1 (14.1%)	0.009
2022	356 (13.2%)	66 (11%)	290 (13.8%)	0.085	346.6 (12.9%)	73.6 (12.5%)	273 (13.1%)	0.018

	Before trimming and weighting				After trimming and weighting			
2023	362 (13.4%)	99 (16.5%)	263 (12.5%)	0.113	364.8 (13.6%)	83.8 (14.2%)	281 (13.5%)	0.021
Season, n(%)								
winter	691 (25.6%)	143 (23.8%)	548 (26.1%)	0.053	679.0 (25.4%)	146.5 (24.8%)	532.5 (25.5%)	0.016
spring	761 (28.2%)	157 (26.2%)	604 (28.8%)	0.058	752.5 (28.1%)	165.9 (28.1%)	586.6 (28.1%)	0
summer	532 (19.7%)	123 (20.5%)	409 (19.5%)	0.025	525.3 (19.6%)	114.8 (19.5%)	410.5 (19.7%)	0.005
autumn	555 (20.6%)	177 (29.5%)	538 (25.6%)	0.087	720.4 (26.9%)	162.8 (27.6%)	557.6 (26.7%)	0.02
Comorbidities, n(%)								
Diabetes	33 (1.2%)	14 (2.3%)	19 (0.9%)	0.113	30 (1.1%)	7.3 (1.2%)	22.7 (1.1%)	0.014
Rheumatological diseases	83 (3.1%)	23 (3.8%)	60 (2.9%)	0.054	81.4 (3.0%)	17.2 (2.9%)	64.2 (3.1%)	0.01
Malignancies	<5 (NR)	0 (NR)	<5 (NR)		0 (NR)	0 (NR)	0 (NR)	0
Cardiovascular diseases	85 (3.2%)	18 (3%)	67 (3.2%)	0.011	85.0 (3.2%)	19 (3.2%)	66 (3.2%)	0.003
Intellectual disability	<17 (<0.6%)	<5 (NR)	12 (0.6%)		<5 (NR)	<5 (NR)	NR	
Congenital malformations	0 (NR)	0 (NR)	0 (NR)	0	0 (NR)	0 (NR)	0 (NR)	0
Psychotropic drugs	214 (7.9%)	59 (9.8%)	155 (7.4%)	0.087	206.2 (7.7%)	44.8 (7.6%)	161.4 (7.7%)	0.005
Asthma exacerbations, n(%)								
0	1056 (39.2%)	211 (35.2%)	845 (40.3%)	0.105	1047.1 (39.1%)	228.5 (38.7%)	818.6 (39.2%)	0.01

	Before trimming and weighting				After trimming and weighting			
1-2	1010 (37.5%)	219 (36.5%)	791 (37.7%)	0.025	1001.4 (37.4%)	220.6 (37.4%)	780.8 (37.4%)	0
>=3	633 (23.5%)	170 (28.3%)	463 (22.1%)	0.145	628.8 (23.5%)	140.9 (23.9%)	487.9 (23.4%)	0.012
Healthcare use during washout, median (IQR)								
Number of hospital days, n(%)								
0	2526 (93.7%)	573 (95.5%)	1953 (93%)	0.106	2510.2 (93.8%)	554.7 (94%)	1956.2 (93.7%)	0.012
1-2	96 (3.6%)	11 (1.8%)	85 (4%)	0.131	91.8 (3.4%)	19.2 (3.3%)	72.6 (3.5%)	0.012
>=3	77 (2.9%)	16 (2.7%)	61 (2.9%)	0.015	74.6 (2.8%)	16.1 (2.7%)	58.5 (2.8%)	0.004
Number of outpatient visits, n(%)								
0-5	492 (18.2%)	122 (20.3%)	370 (17.6%)	0.069	490.5 (18.3%)	110.6 (18.7%)	379.9 (18.2%)	0.014
6-12	938 (34.8%)	175 (29.2%)	763 (36.4%)	0.154	923.5 (34.5%)	198.2 (33.6%)	725.3 (34.7%)	0.024
13-24	887 (32.9%)	218 (36.3%)	669 (31.9%)	0.094	886.7 (33.1%)	200.4 (34%)	686.3 (32.9%)	0.023
>=25	382 (14.2%)	85 (14.2%)	297 (14.1%)	0	376.6 (14.1%)	80.8 (13.7%)	295.8 (14.2%)	0.014
Medication use during washout, n (%)								
Oral corticosteroids	196 (7.3%)	42 (7%)	154 (7.3%)	0.013	193 (7.2%)	193.0 (7.2%)	149.4 (7.2%)	0.009

	Before trimming and weighting				After trimming and weighting			
Biologicals	<5 (NR)	0 (NR)	<5 (NR)		0 (NR)	0 (NR)	0 (NR)	0
Short-acting beta2-agonists (SABA)	2316 (85.9%)	500 (83.3%)	1816 (86.5%)	0.089	2290.3 (85.0%)	2290.3 (85.5%)	1788.8 (85.7%)	0.02
Short-acting muscarinic receptor antagonist (SAMA)		<5 (NR)	13 (1.6%)		<5 (NR)	<5 (NR)	NR	
Leukotriene receptor antagonists	583 (21.6%)	125 (20.8%)	458 (21.8%)	0.024	585.9 (21.7%)	585.9 (21.9%)	453.9 (21.7%)	0.015
Antibiotic use	692 (25.7%)	129 (21.5%)	563 (26.8%)	0.125	689.2 (25.5%)	689.2 (25.7%)	536.5 (25.7%)	0.004
Pneumococcal vaccination	<5 (NR)	<5 (NR)	<5 (NR)		<5 (NR)	<5 (NR)	<5 (NR)	
Influenza vaccination	580 (21.5%)	116 (19.3%)	464 (22.1%)	0.068	574.8 (21.3%)	574.8 (21.5%)	447.3 (21.4%)	0.004

For all comorbidities and co-medications, absence of a record is considered absence of the corresponding comorbidity/co-medication.
All values are presented without imputation.
NR = not reportable
IQR = interquartile range

*For continuous variables aSD was calculated as the absolute difference in group means divided by the pooled standard deviation. For categorical variables, each level was treated as a binary indicator and the aSD is calculated as the absolute difference in proportions divided by the standard deviation of the difference of the two proportions; consequently for categorical covariates aSD is reported per level.

10.3. *Outcome Descriptive Summary Statistics*

Table 21 shows the follow-up time, intercurrent events, and reasons for censoring by treatment group for the primary estimand and estimand 2 in the Finnish registers and UK CPRD. Median follow-up time was 11 person-months (IQR 5–24.3) for V+FF group and 7 person-months (IQR 4–16) for other ICS+LABA group in Finland, and 3.4 person-months (IQR 2-8) and 3 person-months (IQR 2-5.3), respectively, in UK CPRD. In UK CPRD the most common reason for censoring was treatment discontinuation in both groups (occurring in 82.8 % of V+FF initiators and 84.5 % of other ICS+LABA initiators). In Finland, the most common reasons for censoring were treatment discontinuation (52.2 % in V+FF group and 71.5 % in other ICS+LABA group) and end of data instance (17.7 % in V+FF group and 10.8 % in other ICS+LABA group).

Estimand 3 was similar to estimand 1, the only difference being that a composite strategy was used to handle the intercurrent event of death due to pneumonia. It was to be estimated only in FinReg, as causes of death are not available from CPRD. Because no deaths occurred in the study population, the follow-up time, intercurrent events, and reasons for censoring by treatment group for estimand 3 were identical to those obtained for the primary estimand (Table 21). Therefore, estimand 3 was not computed.

Table 21. Follow-up time, intercurrent events, and reasons for censoring by treatment group (vilanterol-fluticasone furoate: V+FF and other ICS-LABA) for primary estimand in Finnish registers and UK CPRD

	Overall		V+FF		ICS+LABA	
	N (%)	Median time in months to censoring event (IQR, min, max)	N (%)	Median time in months to censoring event (IQR, min, max)	N (%)	Median time in months to censoring event (IQR, min, max)
FINLAND						
Person-months of follow-up						
Median (IQR)		7.3 (4-18.3)		11 (5–24.3)		7 (4–16)
Min, max		0, 24.3		0.3, 24.3		0, 24.3
Reasons for end of follow-up						
Treatment discontinuation	1813 (67.2%)	5 (3.9-10, 0, 24.3)	313 (52.2 %)	7 (4–12, 0.8, 23.3)	1500 (71.5 %)	5 (3.9–9, 0, 24.3)
Death	0 (0%)		0 (0 %)		0 (0 %)	
Disenrollment or migration	< 5	6.4 (6.4-6.4, 6.4, 6.4)	<5	6.4 (6.4–6.4, 6.4, 6.4)	0 (0 %)	

	Overall		V+FF		ICS+LABA	
	N (%)	Median time in months to censoring event (IQR, min, max)	N (%)	Median time in months to censoring event (IQR, min, max)	N (%)	Median time in months to censoring event (IQR, min, max)
Pneumonia	18 (0.7%)	6.2 (3.4-12.3, 1.5, 22.9)	6 (1 %)	6.3 (5–11.5, 4.5, 14.8)	12 (0.6 %)	5.4 (2.3–11.2, 1.5, 22.9)
End of data instance (31.12.2023)	332 (12.3%)	7.8 (2.9-12.7, 0.3, 24.3)	106 (17.7 %)	7.9 (3.4–12.5, 0.3, 24.3)	226 (10.8 %)	7.5 (2.7–12.9, 0.4, 24.2)
UK CPRD						
Person-months of follow-up						
Median (IQR)		3 (2-5.5)		3.4 (2-8)		3 (2-5.3)
Min, max		0, 24.3		0, 24.3		0, 24.3
Reasons for end of follow-up						
Treatment discontinuation	7311 (84.4%)	3 (2-5, 0, 24.1)	511 (82.8%)	3.1 (2-6.3, 0.3, 24.1)	6800 (84.5%)	3 (2-5, 0, 24)
Death	< 5	14.4 (11.7-17.2, 8.9, 20)	0 (%)		<5	14.4 (11.7-17.2, 8.9, 20)
Disenrollment or migration	135 (1.6%)	4.2 (1.6-10.1, 0, 24.3)	13 (2.1%)	2.9 (1.8-9.1, 0, 19.6)	122 (1.5%)	4.3 (1.6-10.1, 0, 24.3)
Pneumonia	<10	3.1 (2.1-6.5, 0.3, 23.7)	<5	2.3 (2.3-2.3, 2.3, 2.3)	6 (0.1%)	3.5 (2.2-7.8, 0.3, 23.7)
End of data instance (16.9.2024)	0 (0%)		0 (0%)		0 (0%)	

IQR = interquartile range

The number of pneumonia events was very low in both groups: <5 among V+FF initiators and 6 among other ICS+LABA initiators in UK CPRD, 6 and 12, in Finland, respectively (222). Total follow-up time accumulated across all patients in UK CPRD was 3396.16 person-years in the other ICS+LABA group and could not be reported for the V+FF group because of small number of pneumonia events. Corresponding numbers in Finland were 1748.57person years in other ICS+LABA group and 649.29 person years in V+FF group. Pneumonia incidence rates per 100 person-years were 0.31 (95% CI 0.00–1.70) among V+FF initiators and 0.18 (95% CI 0.10–0.40) among other ICS+LABA initiators in UK CPRD, with corresponding rates being 0.92 (95% CI 0.30-2.00) and 0.68 (95% CI 0.40-1.20) in Finland.

22Table 232. Incidence rates and crude and IPT-weighed hazard ratios for time to first pneumonia in adolescent asthma patients initiating with vilanterol-fluticasone furoate single device combination treatment compared with initiators of other single device inhaled corticosteroid+long-acting beta agonist (ICS+LABA) combination treatments

	No. of persons	No. of pneumonia events	Total follow-up time accumulated across all patients	Pneumonia rate (100 person-years), 95% CI)	Unadjusted HR, 95% CI	IPT-weighted HR, 95% CI*
Finland						
Comparison (other ICS+LABA)	2089	12	1748.57	0.69, 0.40-1.20	1.00 (reference)	1.00 (reference)
Vilanterol-fluticasone furoate	598	6	649.29	0.92, 0.30-2.00	1.35, 0.51-3.56	1.51, 0.56-4.08
UK CPRD						
Comparison (other ICS+LABA)	8049	6	3396.16	0.18, 0.10–0.40	1.00 (reference)	1.00 (reference)
Vilanterol-fluticasone furoate	617	<5	NR	0.31, 0.00–1.70	1.79, 0.21–15.42	3.00, 0.34–26.25
Combined Finland and UK CPRD						
Comparison (other ICS+LABA)	10148	18	5144.8	0.35, 0.21-0.55	1.00 (reference)	1.00 (reference)
Vilanterol-fluticasone furoate	1217	NR	NR	NR	1.41, 0.58–3.43	1.70, 0.69–4.20

*stabilised weights with no truncation in CPRD and with trimming in FinReg, covariates include age, sex, season, diabetes, rheumatological diseases, malignancies, cardiovascular diseases, intellectual disability, congenital malformations, psychotropic drugs, hospitalized asthma exacerbations, oral corticosteroids, biologicals, SABA, SAMA, leukotriene receptor antagonists, antibiotic use, pneumococcal vaccination, influenza vaccination, calendar year of initiation, number of primary care admissions and hospital days

NR = not reportable

10.4. *Primary Estimand*

10.4.1. Primary analyses

22 shows crude and IPT-weighed hazard ratios for time to first pneumonia among V+FF initiators compared with initiators of other ICS+LABA. In UK CPRD, the unadjusted HR was 1.79 (95% CI 0.21–15.42), and the IPT-weighted HR was 3.00 (95% CI 0.34–26.25). In Finland, the corresponding HRs were 1.35 (95% CI 0.51-3.56) and 1.51 (95% CI 0.56-4.08). Because of the very small number of events, these estimates were imprecise and there was no clear evidence of a difference in hazard of pneumonia between the two treatment groups.

10.4.2. Sensitivity analyses

Table 243 presents results of the sensitivity analyses which included IPC-weighted analysis and four best-case/worst-case scenarios assessing the robustness of the findings to censoring at random assumptions made in the primary analysis, and probabilistic bias analysis assessing exposure misclassification.

Table 243. Comparison of hazard ratios and 95% CIs from main analysis and sensitivity analyses accounting for nonrandom censoring by IPC-weighting and "best" and "worst case" scenarios, sensitivity analyses for nondifferential exposure misclassification by quantitative bias assessment

	main estimand IPT-weighted*	Sensitivity analysis 1a: IPT- and IPC-weighted**	Best-case / worst-case scenario 1 (Maximally favors V+FF)	Best-case / worst-case scenario 2 (Maximally favors Other ICS + LABA)	Best-case / worst-case scenario 3 (Optimistic for both groups)	Best-case / worst-case scenario 4 (Pessimistic for both groups)	Sensitivity analysis 2: nondifferential exposure misclassification, IPT-weighted*
Finland							
Comparison (other ICS+LABA)	1.00 (reference)	1.00 (reference	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Vilanterol-fluticasone furoate	1.51, 0.56-4.08	NR	1.51, 0.56-4.08	1.74, 0.67-4.46	1.51, 0.56-4.08	1.74, 0.67-4.46	1.59, 0.59-4.29
UK CPRD							
Comparison (other ICS+LABA)	1.00 (reference)	1.00 (reference	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Vilanterol-fluticasone furoate	3.00, 0.34-26.25	1.01, 0.54-1.92	0.13, 0.02-0.92	25.17, 9.39-67.46	3.00, 0.34-26.22	1.09, 0.59-1.99	NR
Combined Finland and UK CPRD							

	main estimand IPT-weighted*	Sensitivity analysis 1a: IPT- and IPC-weighted**	Best-case / worst-case scenario 1 (Maximally favors V+FF)	Best-case / worst-case scenario 2 (Maximally favors Other ICS + LABA)	Best-case / worst-case scenario 3 (Optimistic for both groups)	Best-case / worst-case scenario 4 (Pessimistic for both groups)	Sensitivity analysis 2: nondifferential exposure misclassification, IPT-weighted*
Comparison (other ICS+LABA)	1.00 (reference)	1.00 (reference	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference
Vilanterol-fluticasone furoate	1.70, 0.69–4.20	NR	0.90, 0.37-2.17	6.28, 3.17-12.43	1.70, 0.69-4.19	1.24, 0.75-2.08	NR

*stabilised weights with no truncation in CPRD and with trimming in FinReg, covariates include age, sex, season, diabetes, rheumatological diseases, malignancies, cardiovascular diseases, intellectual disability, congenital malformations, psychotropic drugs, hospitalized asthma exacerbations, oral corticosteroids, biologicals, SABA, SAMA, leukotriene receptor antagonists, antibiotic use, pneumococcal vaccination, influenza vaccination, calendar year of initiation, number of primary care admissions and hospital days

**weighted for baseline age, sex, calendar year of initiation, number of outpatient admissions and hospital days and time varying covariates time since index treatment initiation, hospitalized asthma exacerbations, oral corticosteroids, biologicals, SABA, SAMA, leukotriene receptor antagonists, antibiotic use, pneumococcal vaccination, influenza vaccination, upper respiratory tract infections, antihistaminic use and allergic dermatological conditions. Sensitivity analyses apply to the primary estimand only.

NR = not reportable

10.4.2.1. Sensitivity analyses to missing data assumptions

In FinReg, the IPC-weighted sensitivity analyses could not be conducted due to small number of censoring events (n<5 in V+FF, n=0 in the other ICS+ LABA group) because the analysis did not converge. However, as the number of persons censored due to disenrollment or end of residence was so low, it is unlikely the IPC-weighting would have substantially impacted the primary estimand. In CPRD, the IPT-weighting substantially reduced the point estimate closer to 1 (IPC-and IPT-weighted HR 1.01, 95%CI 0.54-1.92). The different best and worse case scenarios show the range of plausible estimates under different extreme missing not at random assumptions. In the pooled analyses, all scenarios except the one favouring maximally the comparison group were consistent with the main result suggesting no difference in the pneumonia hazard between the groups. In FinReg the number of individuals with nonadministrative censoring were low, and the results of difference scenarios were consistent with the main estimand with HRs ranging between 1.51-1.74. In CPRD the number of nonadministrative censored people was larger and there was more variability between the different scenarios with the scenario maximally favouring V+FF suggesting lower hazard of pneumonia in the V+FF group and the scenario maximally favouring the comparison group suggesting higher hazard of pneumonia in the V+FF group. This suggests that the findings may be sensitive to assumptions about censoring. However, interpretation of the sensitivity analyses is limited by the very small number of pneumonia events, particularly in the V+FF group of CPRD.

10.4.2.2. Sensitivity analyses to other modelling assumptions

Results of the sensitivity analysis for nondifferential exposure misclassification could not be calculated for UK CPRD due to masking of small event counts. Therefore sensitivity analyses were not conducted for the pooled results either. In Finland the results of sensitivity analysis 2 accounting for nondifferential exposure misclassification were close to the main analysis (HR, 95%CI in sensitivity analysis 1.59, 0.59-4.29 and 1.51, 0.56-4.08 in the main analysis).

10.5. *Supplemental Estimand(s)*

Table 254 presents results for the supplemental estimand 2 analysis showing restricted mean survival time (RMST) and difference in RMST at two-year follow-up for incident pneumonia among V+FF initiators compared with other ICS+LABA initiators instead of HR in the primary estimand, with identical handling of the intercurrent events in both estimands. Estimand 2 could not be computed in CPRD because the models did not converge due to small number of pneumonia events. In FinReg the RMST was 1.98 months in the V+FF group and 1.99 in the comparison group, with no difference in the mean RMST between the groups (-0.01, 95% CI-0.03 to 0.01). Pooled analyses could not be conducted due to small number of events in CPRD.

Estimand 3 was not calculated, because no censoring due to death occurred and therefore no additional pneumonia cases could have been identified from the causes of death register in FinReg. Thus this estimand would have been identical to the primary estimand.

Table 254. Difference in restricted mean survival time (RMST) at two-year follow-up for incident pneumonia in adolescent asthma patients initiating with vilanterol-fluticasone furoate single device combination treatment compared with initiators of other single device inhaled corticosteroid- long acting beta agonist (ICS+LABA) combination treatments.

	RMST (months)	Difference in RMST, 95% CI unadjusted	Difference in RMST, 95% CI IPT-weighted*	IPT- and IPC-weighted difference in RMST, 95% CI**
Finland				
Comparison (other ICS+LABA)	1.99			
Vilanterol-fluticasone furoate	1.98	-0.00, -0.02 to 0.01	-0.01, -0.03 to 0.01	NR
UK CPRD				
Comparison (other ICS+LABA)	NR			
Vilanterol-fluticasone furoate	NR	NR	NR	NR

*stabilised weights with no truncation in CPRD and with trimming in FinReg, covariates include age, sex, season, diabetes, rheumatological diseases, malignancies, cardiovascular diseases, intellectual disability, congenital malformations, psychotropic drugs, hospitalized asthma exacerbations, oral corticosteroids, biologicals, SABA, SAMA, leukotriene receptor antagonists, antibiotic use, pneumococcal vaccination, influenza vaccination, calendar year of initiation, number of primary care admissions and hospital days

**weighted for baseline age, sex, calendar year of initiation, number of outpatient admissions and hospital days and time varying covariates time since index treatment initiation, hospitalized asthma exacerbations, oral corticosteroids, biologicals, SABA, SAMA, leukotriene receptor antagonists, antibiotic use, pneumococcal vaccination, influenza vaccination, upper respiratory tract infections, antihistaminic use and allergic dermatological conditions. Please note that in the current results, only the baseline values of the time varying covariates are included.

NR = not reportable

11. Additional Analyses

No additional analyses.

12. Discussion

12.1. *Key Results*

This study applied the TTE and estimand frameworks to assess whether V+FF increases the risk of pneumonia compared to other single-device ICS+LABA combinations in adolescent asthma patients in UK (2016-2024) and Finland (2017-2023). The primary estimand assessing the IPT-weighted HR of pneumonia for V+FF vs. other ICS+LABA combination in adolescent asthma patients who were on ICS treatment within the year preceding the initiation, while alive and on treatment (i.e., before treatment discontinuation or switching to another ICS+LABA combination) regardless of using other add-on or rescue medications was 3.00 (95%CI 0.34-26.25) in CPRD and 1.51 (95% CI 0.56-4.08) in Finland providing no evidence of the existence or the absence of a difference between the two groups, with pooled HR of 1.70 (95% CI 0.69-4.20).

The sensitivity analyses of estimand 1, exploring the robustness of results for extreme missing data assumptions were consistent with the main analyses except for the scenario maximally favouring the comparison group that suggested increased HR of pneumonia in the V+FF group. However, this was observed only in CPRD (HR, 95%CI 25.17, 9.39-67.46) where the number of nonadministrative censored people was larger than in FinReg, and the follow-up time was shorter and number of outcome events lower than in FinReg. The scenario maximally favouring V+FF suggested a lower hazard of pneumonia in V+FF initiators in CPRD (HR, 95%CI 0.90, 0.37-2.17) but not in FinReg. The sensitivity analyses for exposure misclassification could be conducted in FinReg only due to low event rate in UK CPRD, and the results in FinReg were consistent with the main analyses.

Estimand 2 compared the difference in 2-year RMST instead of HR showed no difference between the treatment groups in Finland (IPT-weighted mean difference between the V+FF and other ICS+LABA group -0.01 months, 95% CI -0.03 to 0.01). Due to small number of pneumonia events, estimand 2 could not be calculated for UK CPRD.

In the preplanned estimand 3, estimand 1 was modified to include pneumonia deaths in the outcome. However, as in FinReg no deaths occurred in the study population, the censoring distribution and pneumonia rates were identical to the primary estimand, estimand 3 was not computed. This estimand was planned for FinReg only as causes of death data were not available for UK CPRD.

Combining the TTE and estimand frameworks allowed us to define a clear and detailed research question (primary estimand), and facilitated the inclusion of a range of additional analyses to support this estimand and investigate sensitivity of the results to a range of assumptions made in the primary analysis. Whilst the sensitivity analyses in CPRD indicate some sensitivity to assumptions about censoring, the small number of events prevents firm conclusions from being drawn.

Additionally, the estimand framework required us specify precisely which treatment effect was being targeted, a step that proved important given how often adolescents on ICS+LABA may discontinue treatment, switch regimens, or add rescue medication during follow-up; any of which could otherwise leave the treatment effect actually being estimated open to interpretation. By requiring explicit specification of intercurrent events and their handling

strategies, the framework highlighted a point that needed clarification: do we want to compare the risk of pneumonia in V+FF vs other ICS+LABA or in V+FF+rescue medication vs other ICS+LABA+rescue medication? Should a patient initiating rescue medication be considered to have departed from their assigned treatment with their pneumonia risk afterwards being no longer of interest, and thus handled with a while-on-treatment strategy (administratively censored)? Or is the risk still of interest and should such medication use be considered part of the assigned treatment itself, and thus be handled with a treatment-policy strategy, as adopted. Addressing this question directly within the estimand table, allowed us to make this decision explicitly and early in protocol development.

12.2. *Interpretation of results*

These initial pooled results from FinRegistry and CPRD provided no evidence of the existence or the absence of a difference in pneumonia risk between adolescents with asthma who initiated single-device V+FF and those who initiated other single-device ICS+LABA combinations, as the confidence intervals were very wide, ranging from a 31% reduction to a 4.2-fold increase in the IPT-weighted HR in the pooled analyses. In FinReg the HRs were more consistent across the sensitivity analyses, whereas in CPRD the best- and worst- case scenarios implied the results may be sensitive to assumptions about censoring. On the other hand, the results should be interpreted cautiously as highlighted above.

Evidence on pneumonia risk in asthma patients taking V+FF specifically is limited. An integrated analysis of clinical studies assessing safety (and efficacy) on FF showed that pneumonia events were rare in all treatment groups (≤0.7%).[1] However, a pragmatic RCT in adults with asthma reported pneumonia risk as one of its safety outcomes among patients randomised to V+FF or to taking their usual care (ICS or ICS+LABA). [13] Serious adverse events of pneumonia were rare and equal when analysed by actual treatment at the time of event, but numerically higher with V+FF when analysed by the group they were originally randomised to (23 vs 16 events, IR 1.4, 95% CI 0.8–2.7). We note however that these analyses target two different estimands, that is they answer two different questions and results are therefore not expected to be necessarily comparable with the results of this TTE. It should be noted that although comparison in the hypothetical target trial was other ICS+LABA combination, the actual conducted trials have used ICS only as the comparison treatment because those trials were designed to establish the added benefit of the combination versus monotherapy. However, as the use of ICS+LABA combination represents a step-up approach (i.e., it is initiated when adequate symptom control is not achieved with ICS and as-needed SABA), emulation of a trial with ICS only as the comparison group would not be desirable. In addition, challenges in obtaining data on actual asthma severity would further prevent meaningful comparison with ICS only comparison group.

To our knowledge, no specific estimations on use of V+FF combination and risk of pneumonia in adolescents with asthma exist. Few studies have evaluated use of ICS and the risk of pneumonia in children/adolescents with asthma. A previous meta-analysis of RCT evidence on children up to 18 years with asthma found that ICS use did not increase the risk of pneumonia compared to placebo in children with asthma.[14] In addition, a recent case-control study [15] and a recent cohort study [16] on children with asthma, found no evidence that ICS use was associated with risk of pneumonia [15] or hospitalisation for pneumonia [16] in comparison to no ICS use. Kamgang et al [16] also conducted a subgroup analysis of ICS and LABA combination therapy showing HR of hospitalization for pneumonia being 1.18 (95% CI 0.68 to 2.07) compared to episodes of ICS nonuse. However, these previous

studies have limitations, including difficulty to fully account for asthma control and severity in Shrestha et al.[15], and restriction of the outcome to hospitalised pneumonia in Kamgang et al. [16], which may underestimate overall pneumonia risk because many pneumonia cases are diagnosed and treated in outpatient settings. In addition, we set out to evaluate the impact of potential outcome misclassification in estimand 3 including pneumonia ascertained from the causes of death register in FinReg. However, no additional cases were identified from this data source implying that using primary and secondary healthcare diagnoses is sufficient.

12.3. *Limitations*

We designed the TTE to approximate the hypothetical target trial protocol as closely as possible. However, certain limitations arose from challenges in emulating specific aspects and these should be considered when interpreting the results. While developing the TTE protocol we anticipated the asthma severity to be a key confounder which is difficult to directly capture in CPRD and FinReg. We used several proxies (LTRA, biologicals, oral corticosteroids, antibiotics and asthma exacerbations operationalised as asthma hospitalisations or specialised healthcare admission). However, we were not able to reliably ascertain ICS strength prior to beginning of follow-up, and omission of this covariate is a key limitation of the study. However, we explore the possibilities to obtain this information so that it can be adjusted for in future studies. An additional challenge was related to hospitalised asthma exacerbations. In the approved version of the TTE protocol this was operationalised as the number of overnight hopitalisations but was later changed to include also same-day admissions. We note that albeit this allows the capture of e.g. emergency admissions that do not require overnight stay, it leads to overestimation in FinReg as the revised definition also includes the asthma control visits to specialised healthcare policlinics because they are not differentiable in this data source with currently available data. Although this difference manifests as asthma exacerbations being significantly more common in FinReg than UK CPRD, the pattern between V+FF and comparison group is the same in both databases. Further, we expect the misclassification in FinReg to be nondifferential between the treatment groups and the association of exacerbation with treatment/outcome not to deviate from monotony. Hence adjusting for the misclassified confounder will still reduce bias.[17] Alternatively, we may consider this confounder to represent the intensity of asthma care in specialised settings, rather than hospitalised asthma exacerbations in Finland.

A key difference between the hypothetical trial and emulation is the treatment assignment. While this would have been random in the RCT, we emulated it by IPT-weighting the treatment groups based on prescribed medications (UK) and dispensed medications (Finland). Although the weighting resulted in comparable covariate distribution between the groups, it does not account for unmeasured confounders such as household-related related risk factors including exposure to smoking, crowded housing and parental socioeconomic position which remain unaccounted for. In addition to unmeasured confounding, the approach has multiple additional assumptions, such as positivity, consistency, and correct specification of the propensity score model. Violations of any of these assumptions could bias the estimates, and to ensure comparability between the groups we excluded a small number of people in the nonoverlapping ranges of the PS distribution. This is unlikely to impact the generalisability of results due to small number of excluded persons (2 in V+FF and 10 in the other ICS+LABA group), but to improve the comparability of groups. In both data sources,

the information on actual medication use or adherence is not available, which may potentially lead to exposure misclassification. However, this is not per se a deviation from the TTE as nonadherence also occurs in RCTs.

Estimand 1 relied on assumptions about censoring. Although IPC-weighed sensitivity analyses were conducted, and extreme missing-not-at-random scenarios were modelled, the assumptions underlying these methods cannot be verified from the observed data and therefore remain uncertain. The smaller than expected size of study population also prevented us from estimating estimand 2 (RMST) and conducting the sensitivity analyses for exposure misclassification in UK CPRD.

We accounted for the rare outcome event in sample size calculations and included CPRD as one of the data sources to maximise the number of individuals. Still, the number of adolescent asthma patients initiating V+FF during the study period was low, resulting to smaller than expected study populations in both countries. The feasibility assessment evaluated whether the study variables are available with sufficient completeness and temporal coverage to support the research objectives and whether reaching the required sample size appears possible given the known prevalence of adolescent asthma in UK and Finland. However, as the feasibility assessment was conducted prior to data extraction, it was not possible to evaluate whether the expected study size would be reached after applying the specific inclusion/exclusion criteria such as new use, or previous use of ICS as there were no publicly available estimates for these, and such detailed counts are beyond the permitted scope of feasiblity assessment in the data sources we used. Although the V+FF combination was approved for adolescent asthma in EU in November 2013, the number of V+FF initiators compared to initiators of other ICS+LABA combinations during the study years was still low. These findings imply that for special groups such as paediatric or adolescent populations, inclusion of multiple countries may be needed to ensure a sufficient number of exposed participants in new-user designs, even for common conditions such as asthma among paediatric or adolescent populations.

Inclusion and exclusion criteria that had the largest impact on the eligible study population size prior to removing prevalent users were the requirement of ICS treatment in the previous 365 days and asthma diagnosis in the preceding 730 days. While deriving the target population of adolescents with asthma who used ICS in the previous year and had a recorded asthma diagnosis and who were not yet on ICS+LABA combination treatment (beginning of the flowchart in Figure 3) we excluded altogether 4544 people in CPRD as they had no ICS prescription in the preceding year, and 7606 who had no record of asthma diagnosis in 730 days before the index date. In FinReg, 3075 adolescents were excluded due to no ICS dispensing in the preceding year and 1097 with no asthma diagnosis in the preceding 730 days. These exclusions were applied to ensure the population represents adolescents with asthma and to ensure the asthma severity was on a comparable level, i.e., a step-up approach from ICS and as-needed SABA rather than direct initiation of ICS+LABA combination. Interestingly, the asthma inclusion criteria had larger impact in the CPRD data, although a wider codelist, including also more non-specific codes as proposed previously[6], was applied than in Finland. In retrospect, as these medications are primarily used for asthma in adolescent population, a sensitivity analysis without the requirement of asthma diagnosis may have been useful to assess whether this requirement impacts the point estimates or merely the precision of the estimate. In addition, prior to developing the study protocol, a drug utilisation study evaluating the prevalence of asthma diagnosis and treatment trajectories of adolescent asthma patients would have been useful to inform the study design and potentially avoiding exclusions that significantly decrease the sample size but may not be necessary

for validity. Similarly, information on background incidence of pneumonia in these specific populations would have been useful to inform sample size calculations.

The study population was further reduced by the application of one-year washout for the active comparator new-user design. Although this requirement strengthens the likelihood that all study participants are in similar asthma stage, i.e., they initiate the ICS-LABA combination after insufficient symptom control with ICS (and as-needed SABA) rather than switch from one combination treatment to another, it resulted to exclusion of over 50% of the otherwise eligible initiators. However, omitting this exclusion criterion would have likely biased the estimate, and deviated the study population from the target trial.

In addition, the median length of follow up in CPRD was approximately three months, with treatment discontinuation being the most common reason for censoring. In FinReg, discontinuation from treatment was also the most common censoring reason, but the proportions were lower (52.2% in V+FF group and 71.5% in other ICS+LABA compared with >80% observed in both groups in CPRD). Switches from one ICS+LABA combination to another due to insufficient treatment response may account for this partially, but it is also possible that the a priori chosen grace period of 30 days was too short and resulted too often to early termination of treatment episodes, particularly in CPRD which covers prescriptions with no information on the dispensed amount. The typical prescription duration in CPRD is ca. one-month treatment (30 days), and if the dispensed amount was larger, the duration of that specific prescription would be underestimated resulting into too early censoring. This typical dispensing pattern was our rationale for the grace period length. Specifying a longer grace period would also risk including long periods of untreated time as treated, which would undermine the stated “"while on treatment” approach to treatment discontinuation. The short median follow-up also contributed to the observed low number of recorded pneumonia events, particularly in CPRD. In future studies, a priori assessment of drug utilisation patterns would be useful to optimise treatment episode modelling parameters and avoid the introduction of treatment gaps when they do not exist in reality. This is particularly relevant for data sources where the prescription information, but no dispensing data are available.

13. Conclusion

These findings from FinReg and CPRD did not provide evidence of a difference or lack thereof in pneumonia risk between adolescent asthma patients who initiated V+FF and those who initiated other ICS+LABA combinations. The number of adolescent asthma patients initiating V+FF during the study period was low and person-months of follow-up short, resulting to smaller than expected study populations and low number of pneumonia events during follow-up in both countries. This case study shows TTE and estimand frameworks strengthen the planning, designing and conducting of non-interventional studies by enabling more precise definition of the targeted treatment effect. Still, drug utilisation studies prior to TTE can provide meaningful information for defining the inclusion/exclusion criteria so that reductions in sample size are avoided without compromising the (internal) validity of the results, as well as modelling parameters on treatment episode generation. Further, for special groups such as paediatric or adolescent populations and rare outcomes as pneumonia, inclusion of multiple countries is needed to ensure sufficient number of exposed participants in new-user designs, even for common conditions among paediatric or adolescent populations such as asthma.

14. References

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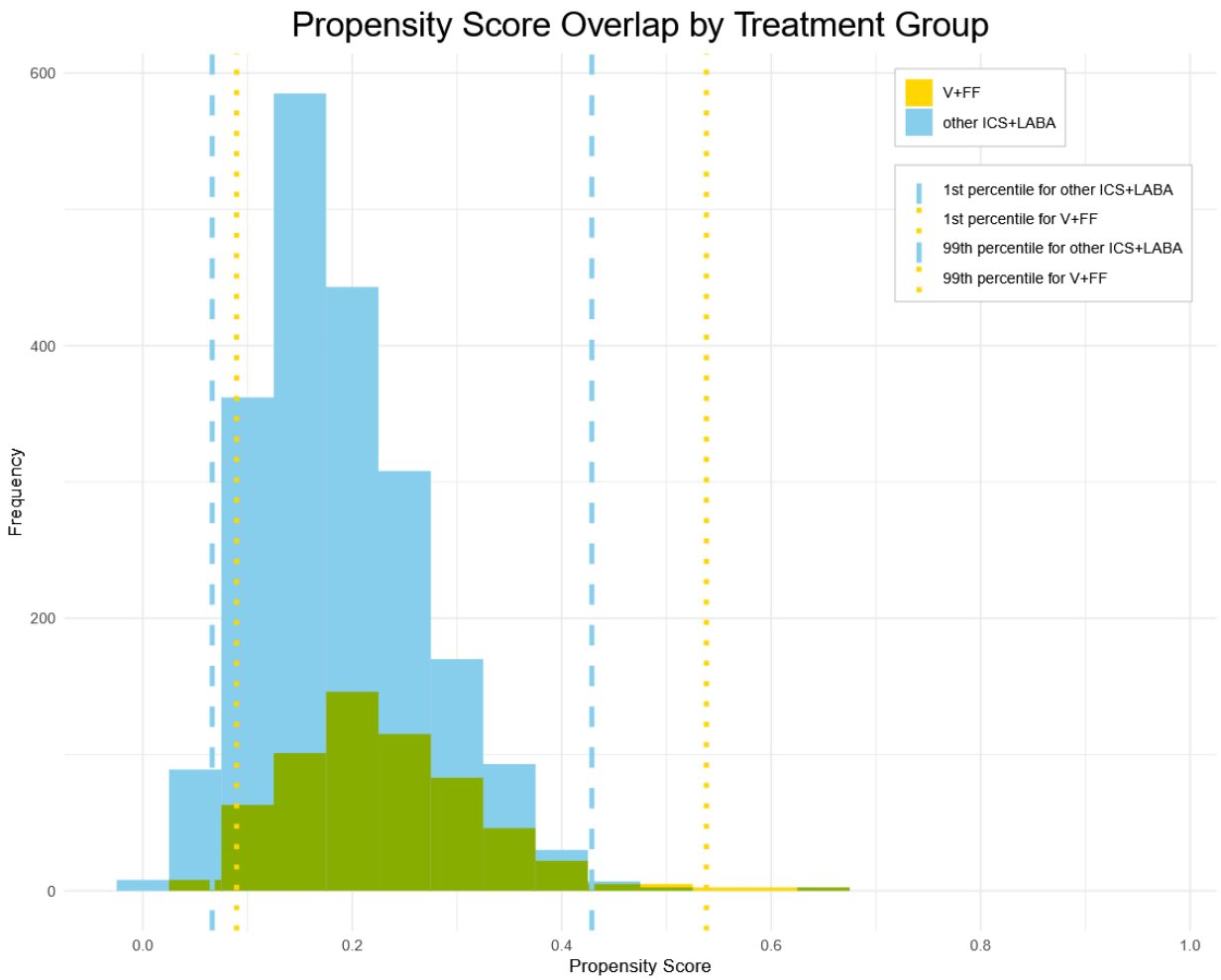
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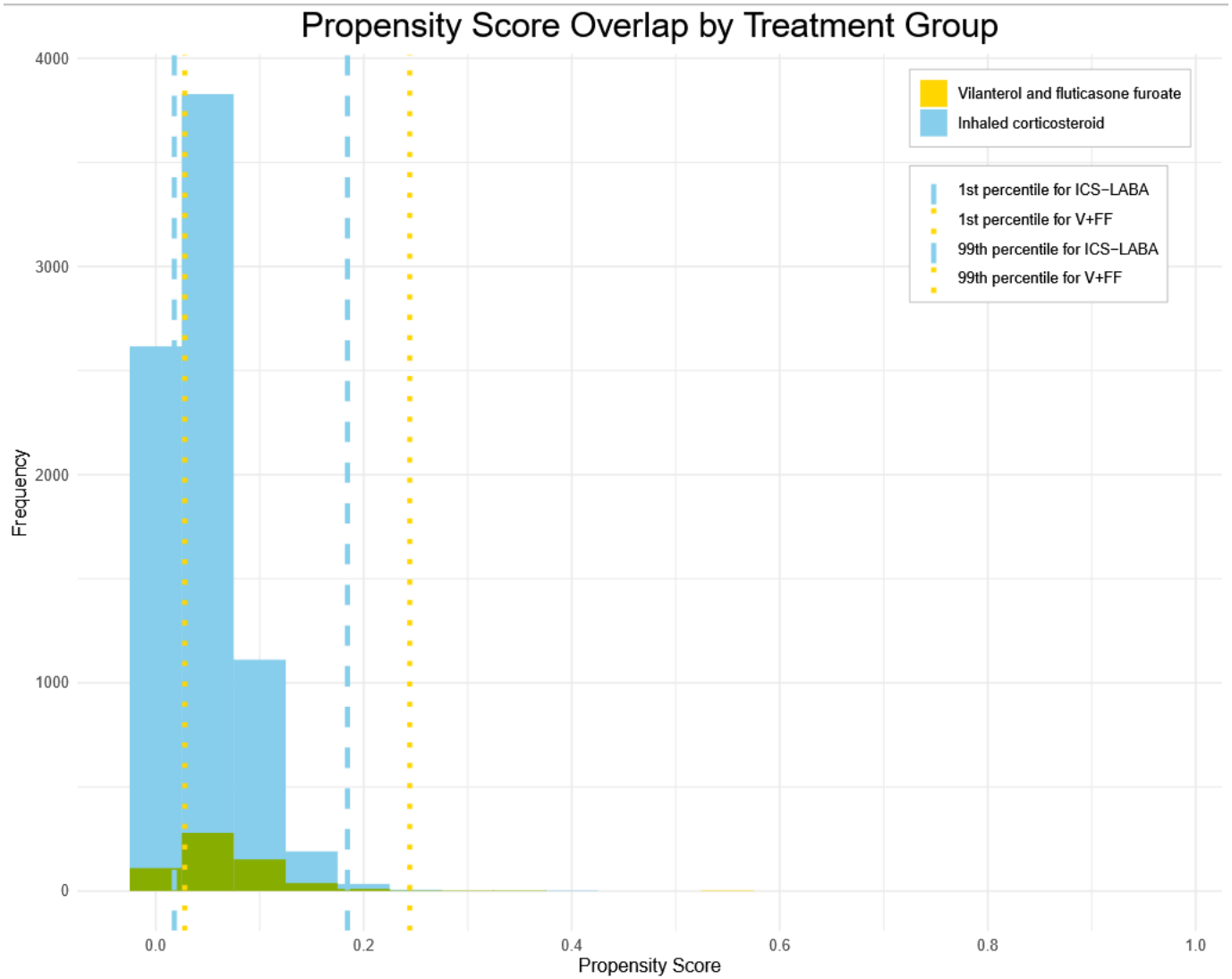
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15. Appendices

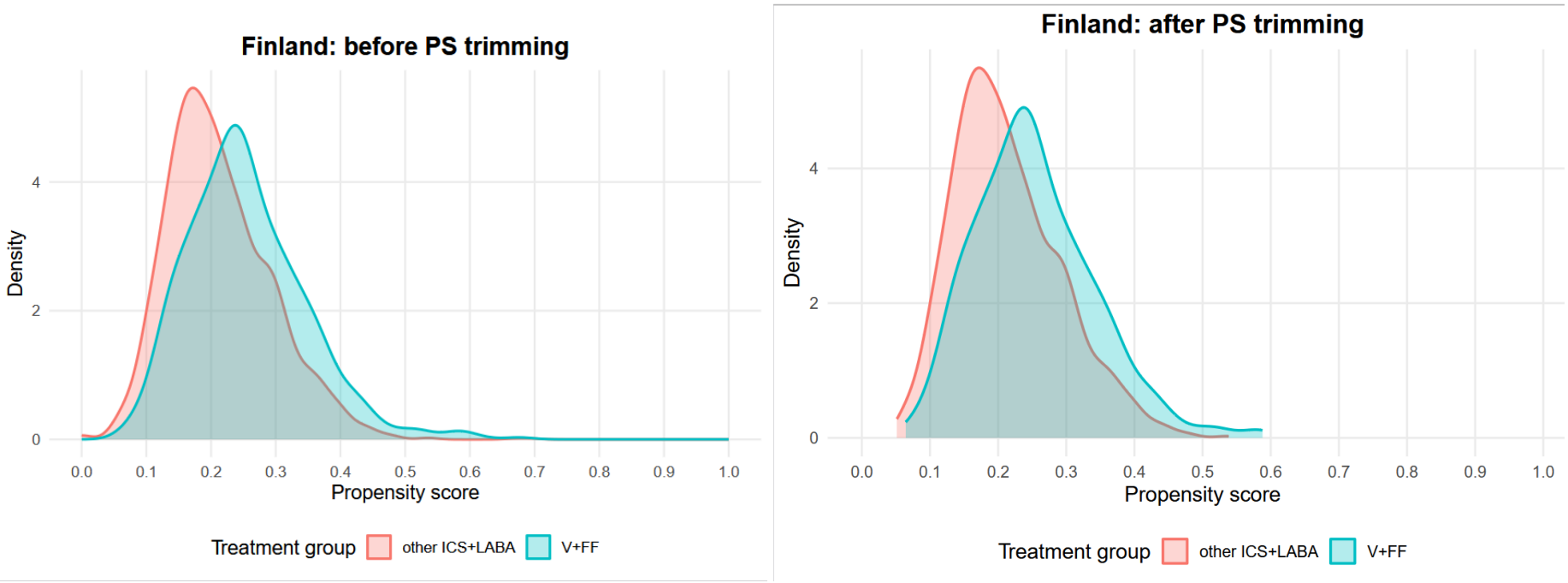
15.1. *Supplemental Tables and Figures*



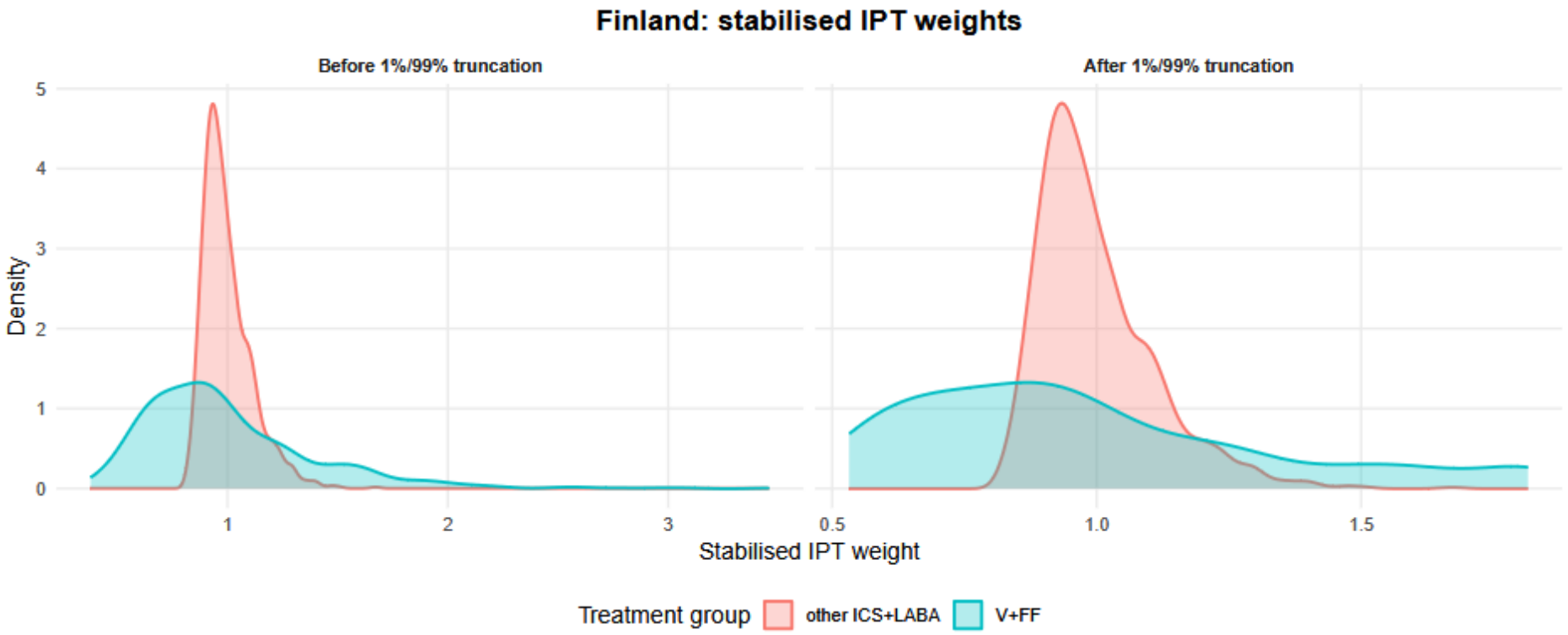
Supplemental Figure 1. Distribution and overlap of propensity scores by treatment group before trimming in Finland.



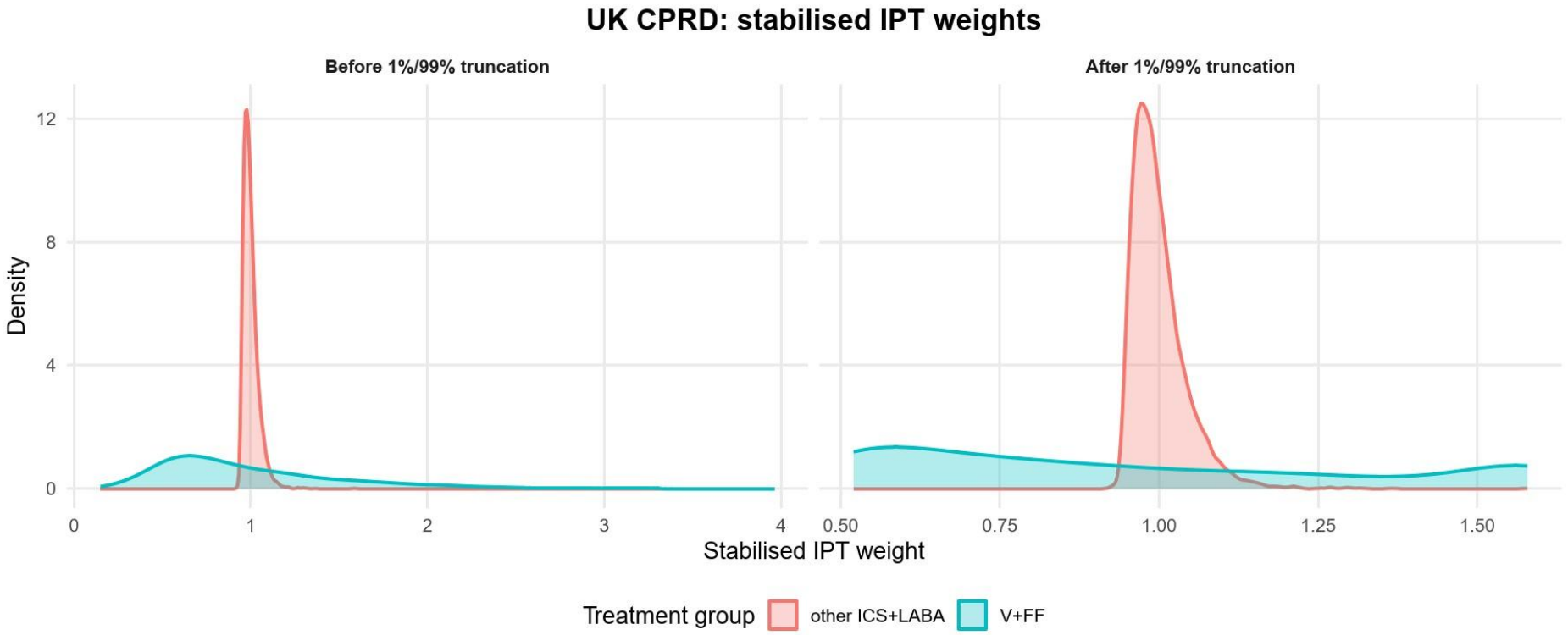
Supplemental Figure 2. Distribution and overlap of propensity scores by treatment group, intervention V+FF in CPRD



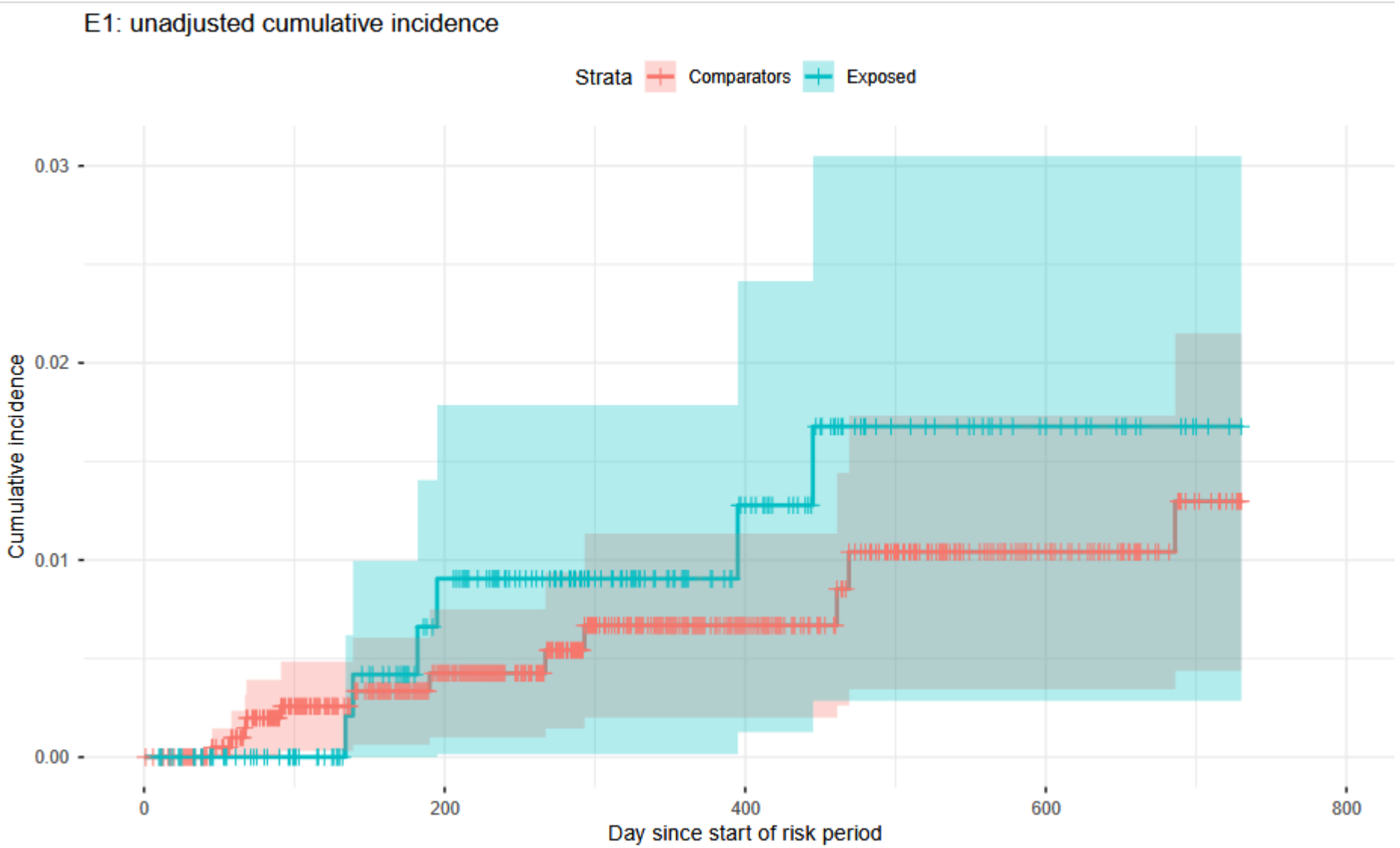
Supplemental Figure 3. Propensity score distribution in FinReg before (left-hand panel) and after (right-hand panel) trimming.



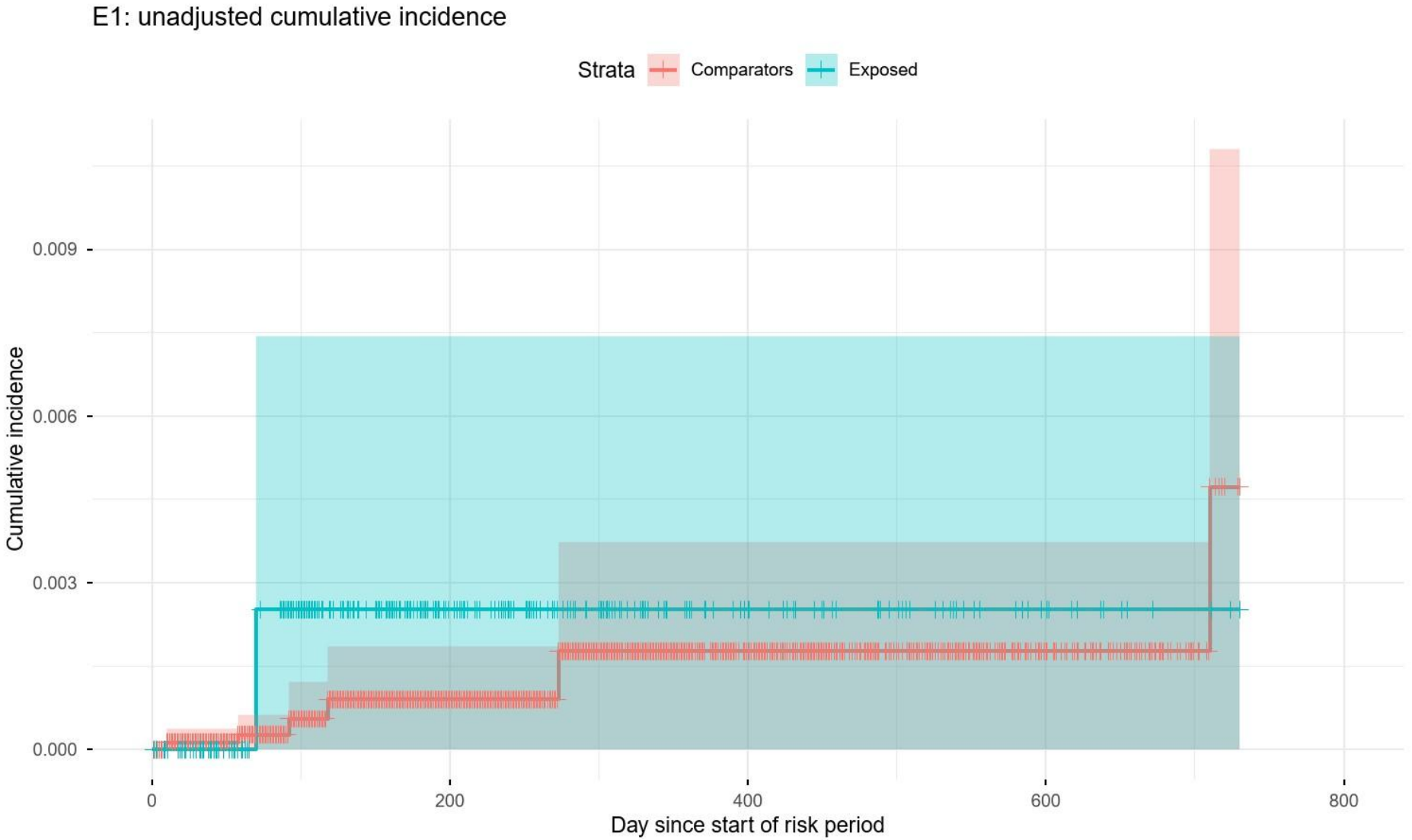
Supplemental Figure 4. Density IPTW weights before (left-hand panel) and after (right-hand panel) truncation at 1 at 99% in FinReg.



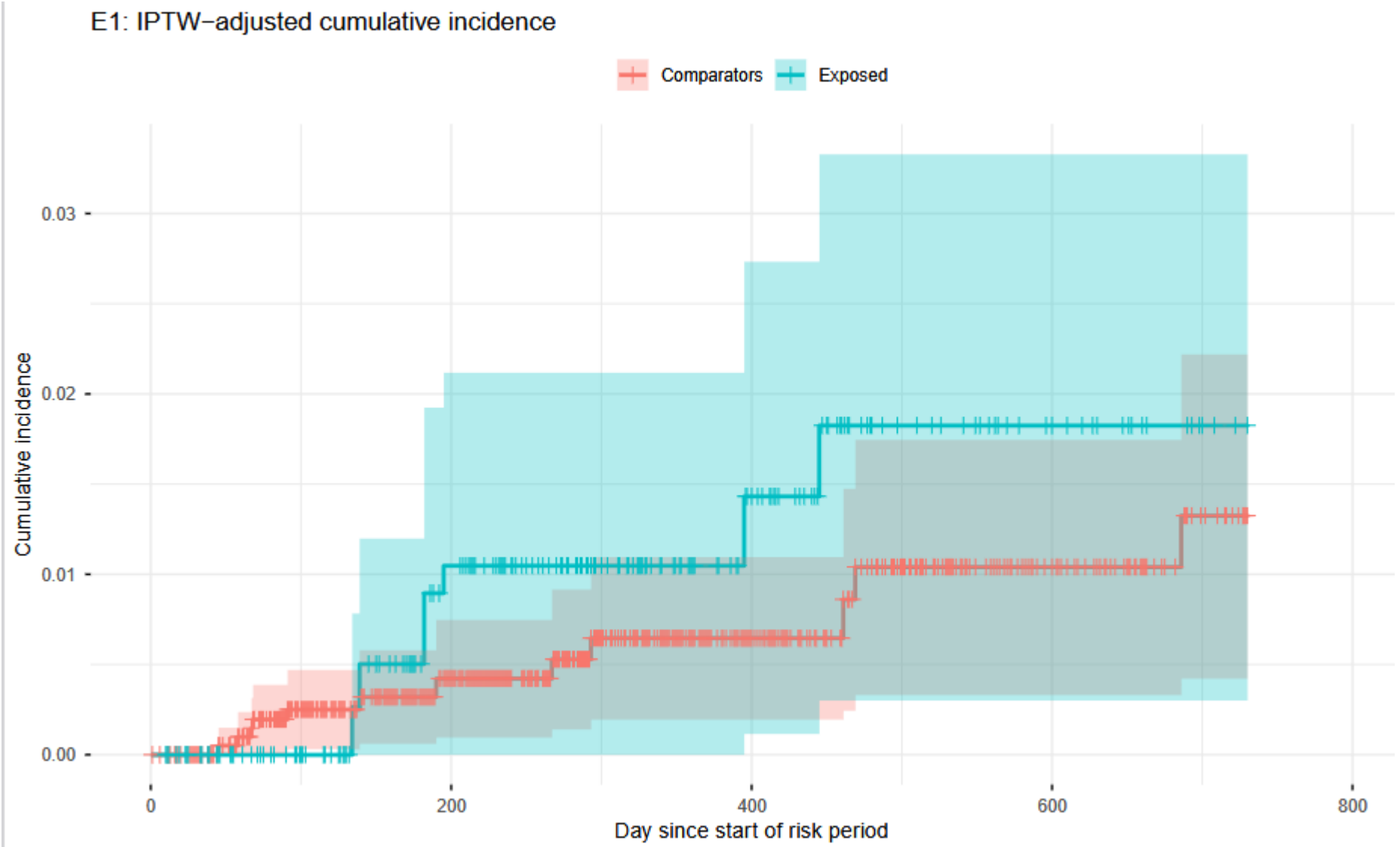
Supplemental Figure 5. Density IPTW weights before (left-hand panel) and after (right-hand panel) truncation at 1 at 99% in CPRD.



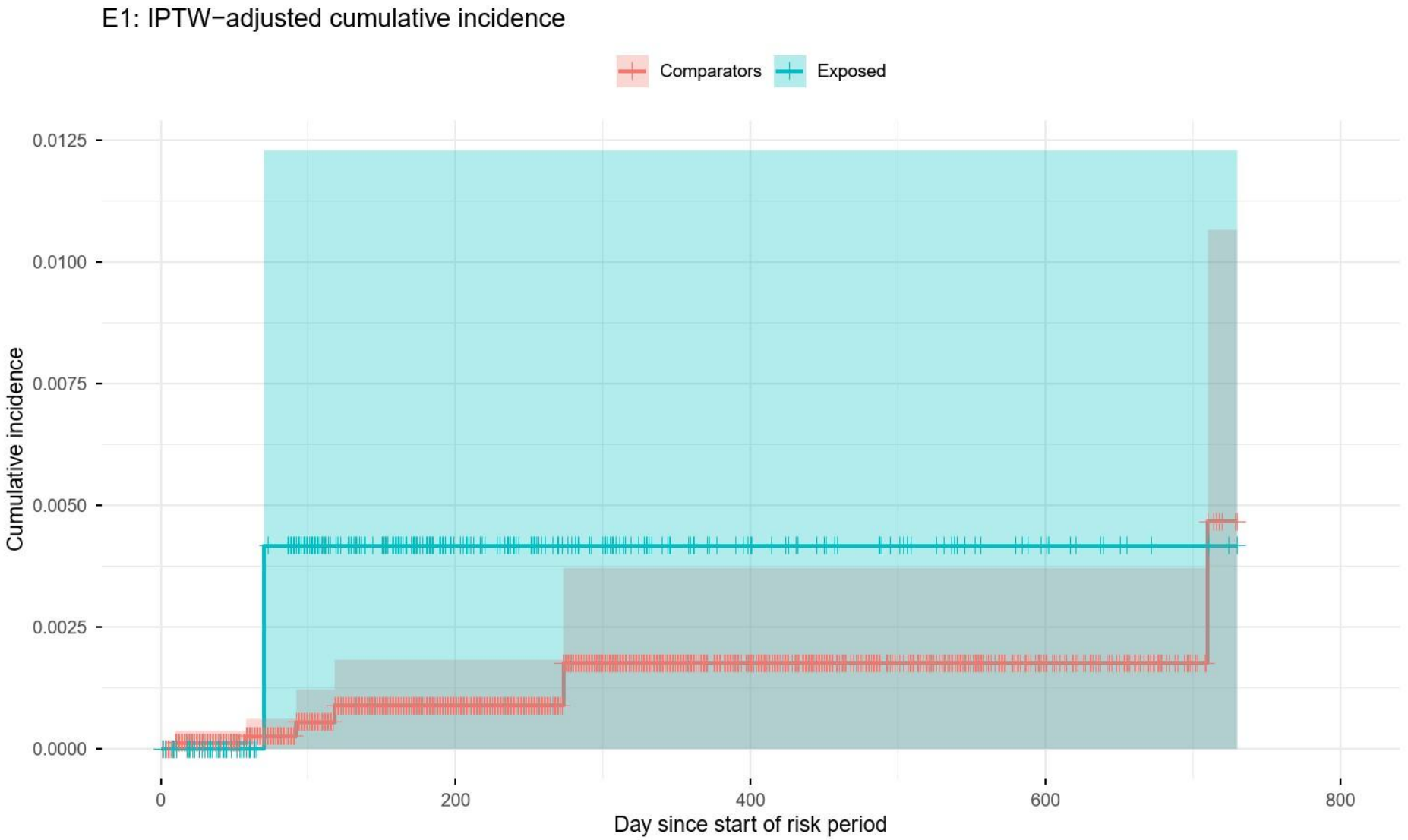
Supplemental Figure 6. Unadjusted cumulative incidence in FinReg.



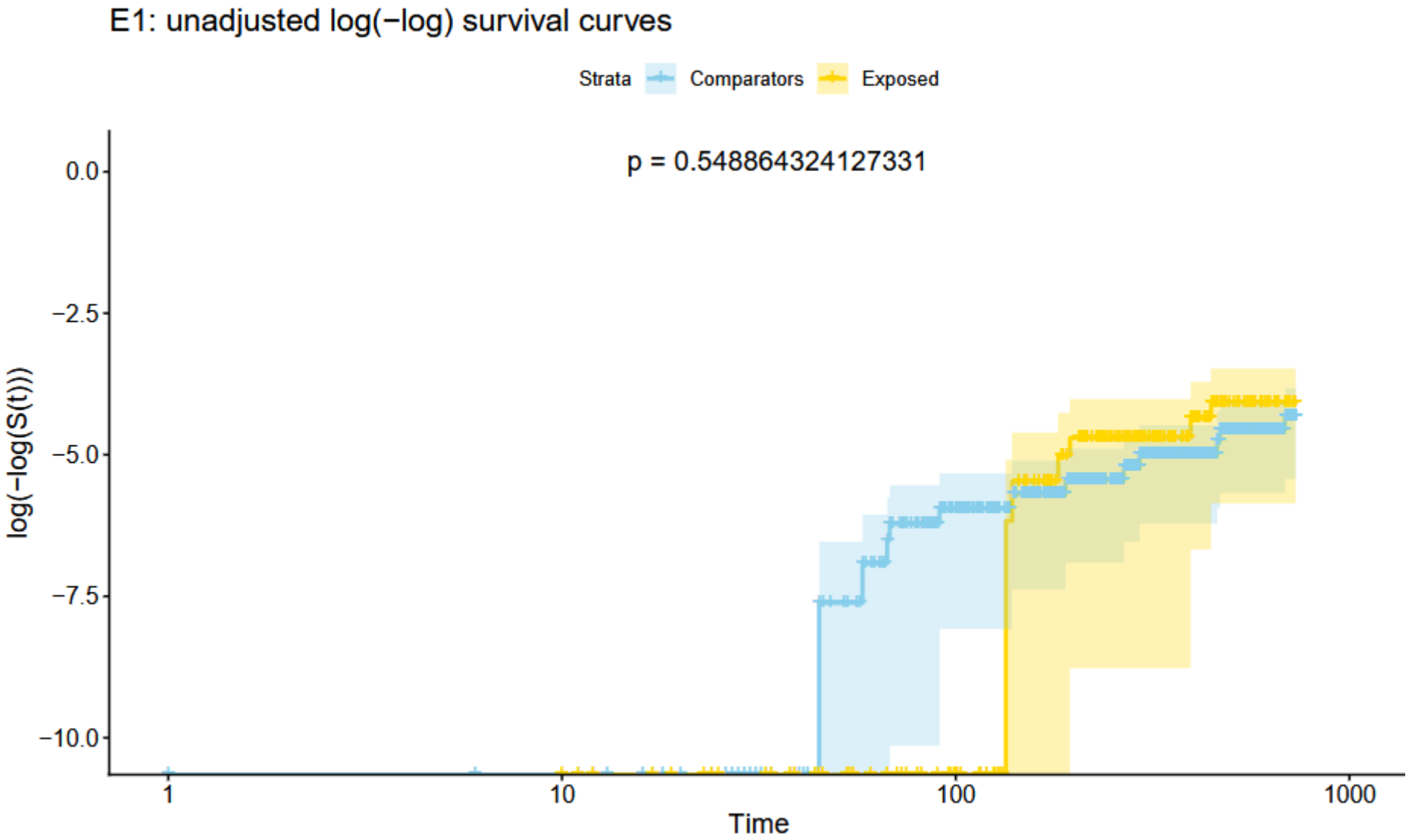
Supplemental Figure 7. Unadjusted cumulative incidence in UK CPRD.



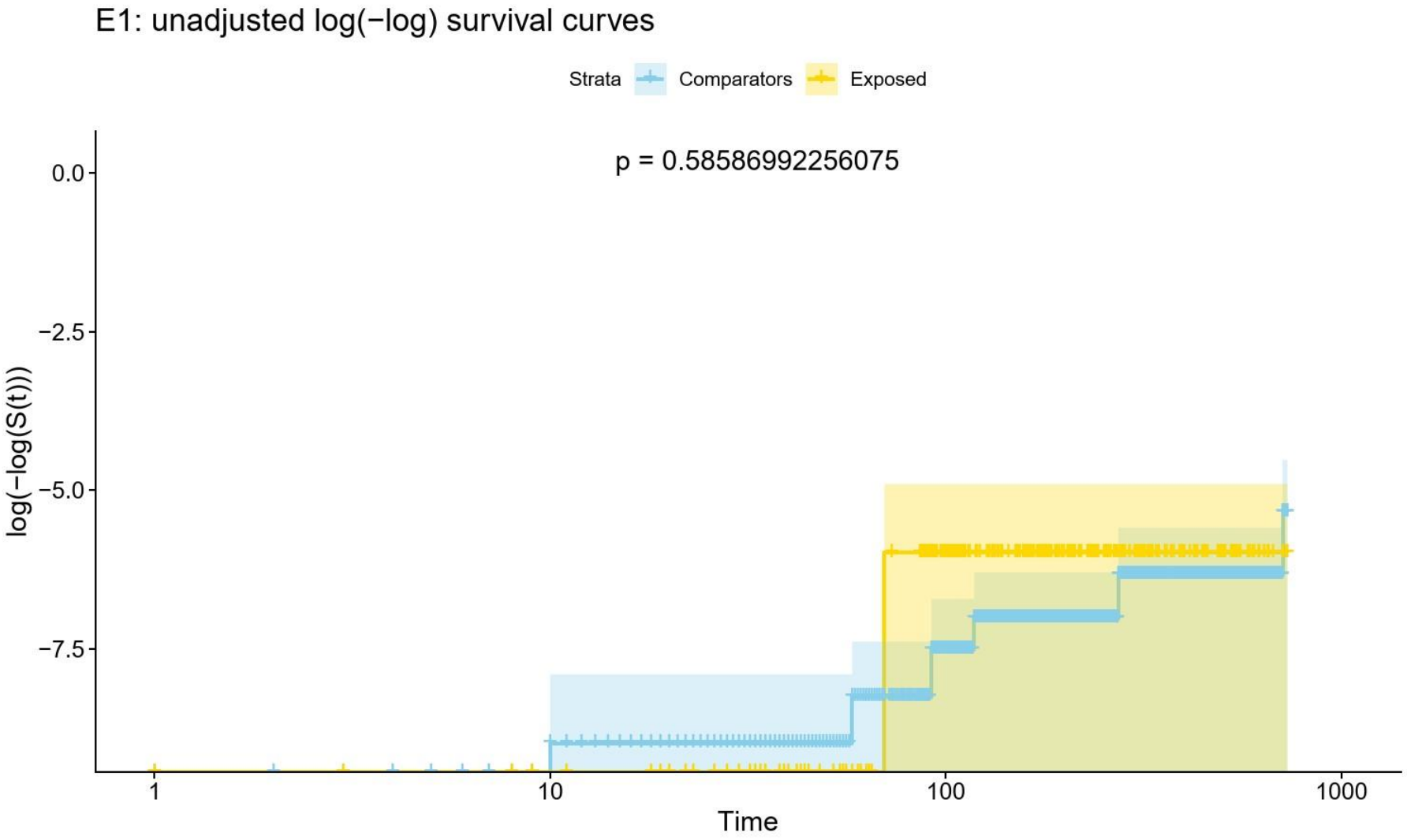
Supplemental Figure 8. IPTW-adjusted cumulative incidence in Finreg



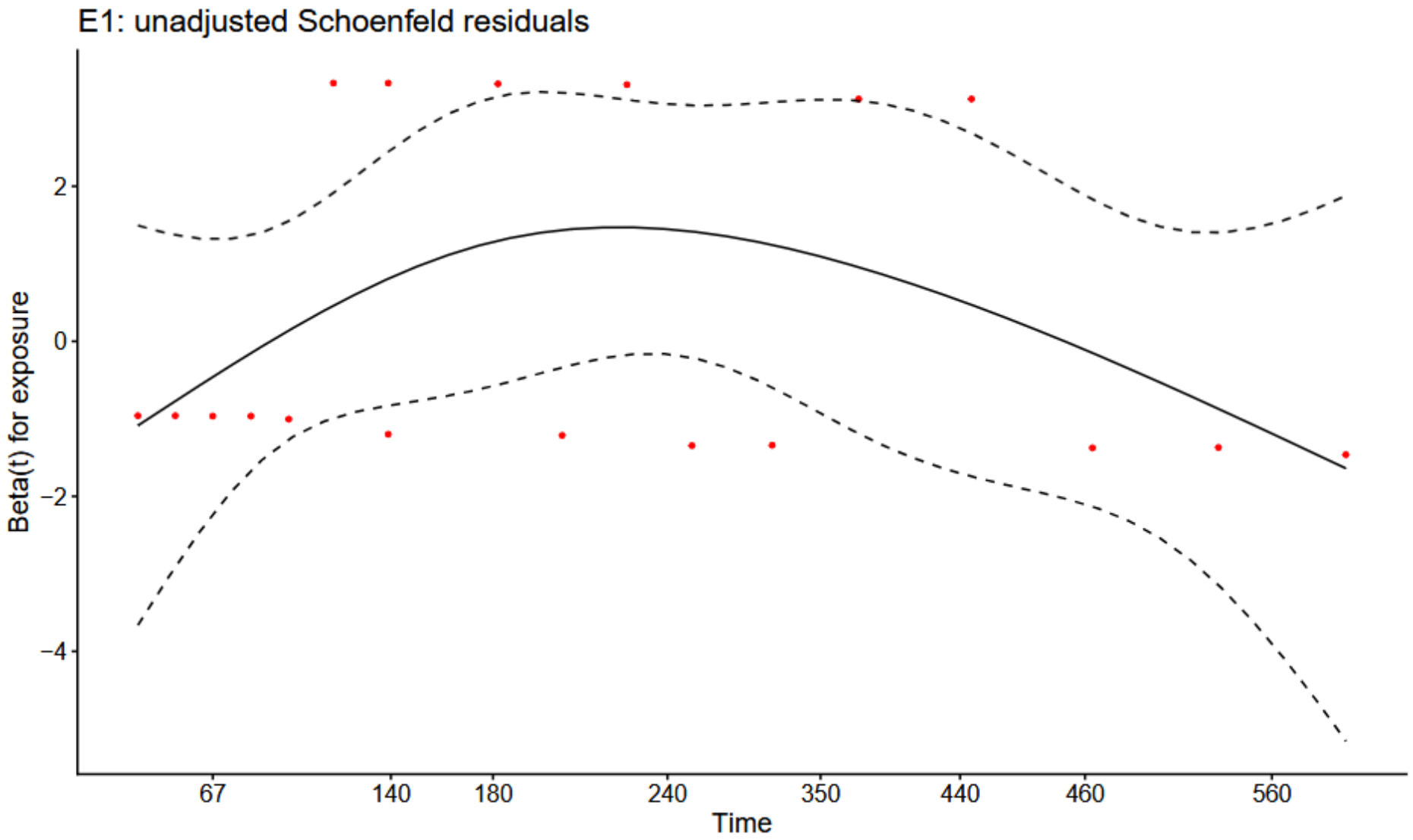
Supplemental Figure 9. Figure IPTW-adjusted cumulative incidence in UK CPRD.



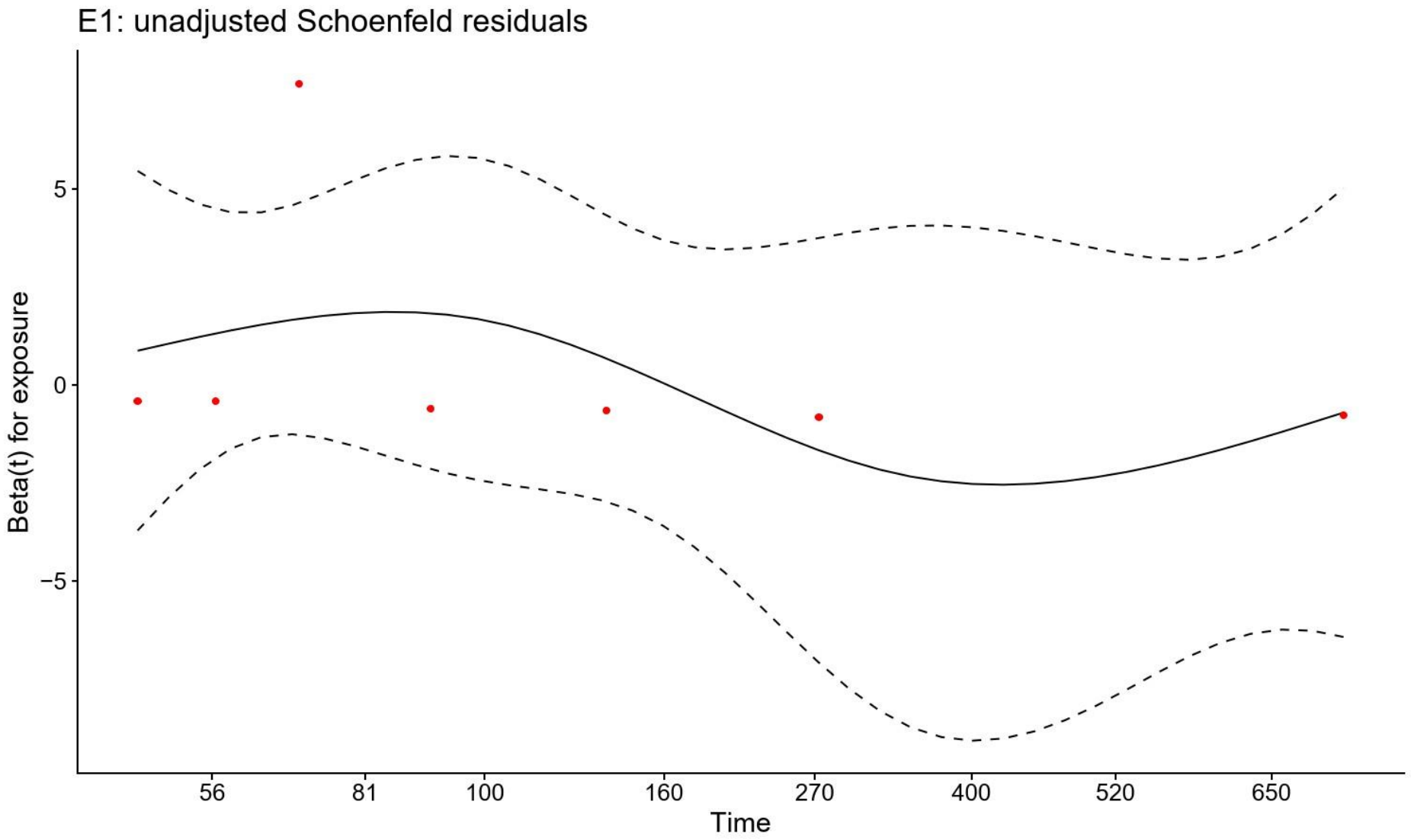
Supplemental Figure 10. Unadjusted log(-log) survival curves in FinReg.



Supplemental Figure 11. Unadjusted log(-log) survival curves in UK CPRD.



Supplemental Figure 12. Unadjusted Schoenfeld residuals in FinReg



Supplemental Figure 13. Unadjusted Schoenfeld residuals in UK CPRD.

15.2. *Precision-Based Sample Size Rationale*

According to sample size calculation for the target trial based on hypothesis testing, a total of 26,750 subjects (13,375 per group) would be needed for a 2-year study with 1% loss to follow-up, to detect a hazard rate difference of 0.0027 (control group hazard 0.0108, experimental group hazard 0.0135, HR 1.25) with 80% power at a 5% significance level, using a conditional test for hazard differences under an exponential survival model. The expected number of events is 635 (283 in the comparison group and 352 in the experimental group).

Estimation of precision

No hypothesis test is performed in this non-interventional study and the focus is on the precision of the estimated treatment effect. Assuming the study size in each RWD source will be similar to the sample size of the target trial, the precision (based on the 95% CI) for a HR from a Cox proportional hazards model, the standard error (SE) of the log(HR) is derived from the total number of events. An additional calculation with 20% lower event rate (508 events) is conducted to evaluate the precision if the event rate is lower than expected.

Assumptions

- Equal allocation to treatment groups.
- Large-sample normal approximation for log(HR).
- Symmetric CI on the log scale.

Supplemental Table 1. Confidence interval widths under different events counts

Scenario	Number of Events	Hazard Ratio (HR)	log(HR)	Standard Error (SE)	Margin of Error	Lower CI (HR)	Upper CI (HR)	CI Width	Precision (upper 95%CI limit/HR -1)
Scenario 1	635	1.25	0.22314355	0.05612135	0.10999785	1.12	1.40	0.28	12%
Scenario 2	508	1.25	0.22314355	0.06274558	0.12298134	1.11	1.41	0.30	12.8%

15.3. *Study Meta data (code lists, code books)*

Metadata related to this case study, including the corresponding codelists and codebooks, can be accessed through Zenodo: CS5_Codelist.