



# THREATENED ABORTION AND THE LONG-TERM HEALTH OF CHILDREN AND MOTHERS

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Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital, Aarhus, Denmark



# ROADMAP

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Background



Aims



Methods



Results



Discussion



Conclusions

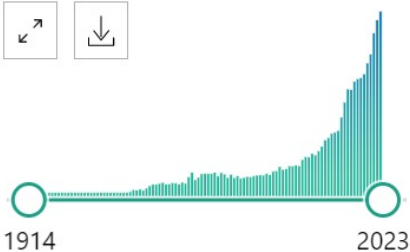


# THREATENED ABORTION



## Preeclampsia

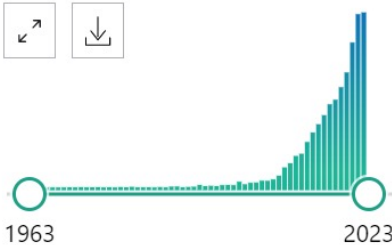
RESULTS BY YEAR



3,275

## Gestational diabetes

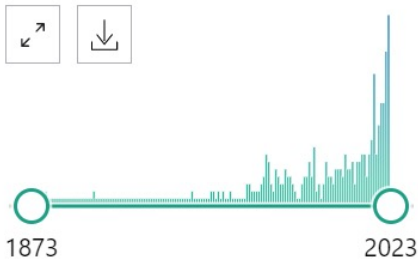
RESULTS BY YEAR



3,010

## Threatened abortion OR vaginal bleeding in pregnancy

RESULTS BY YEAR

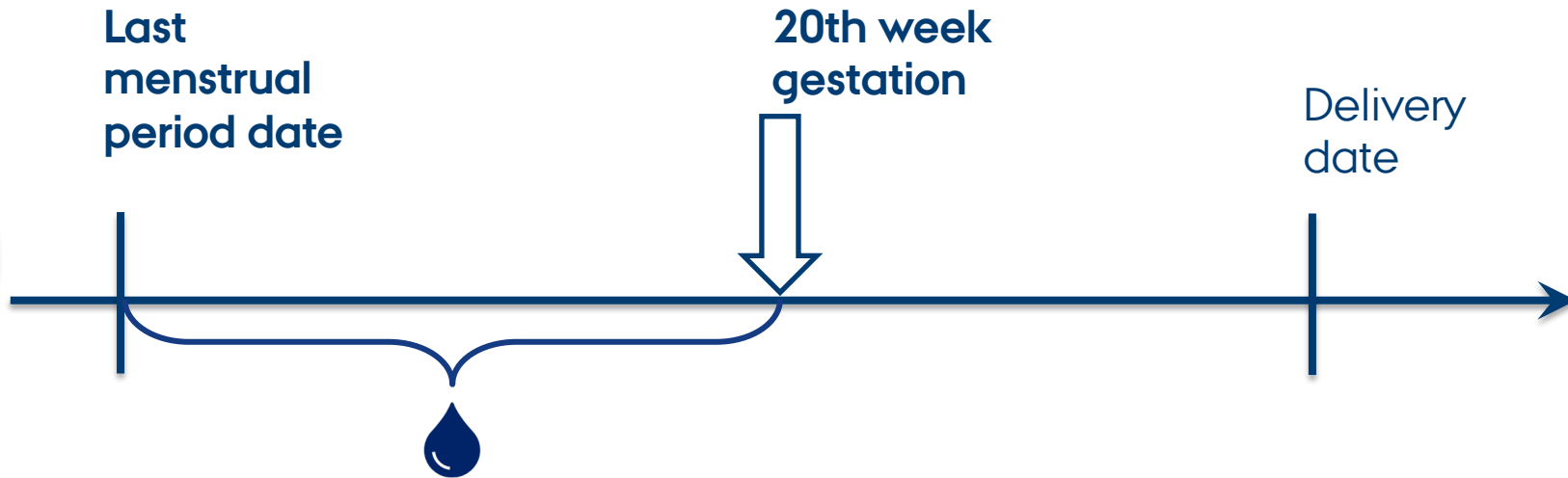


41

# BACKGROUND

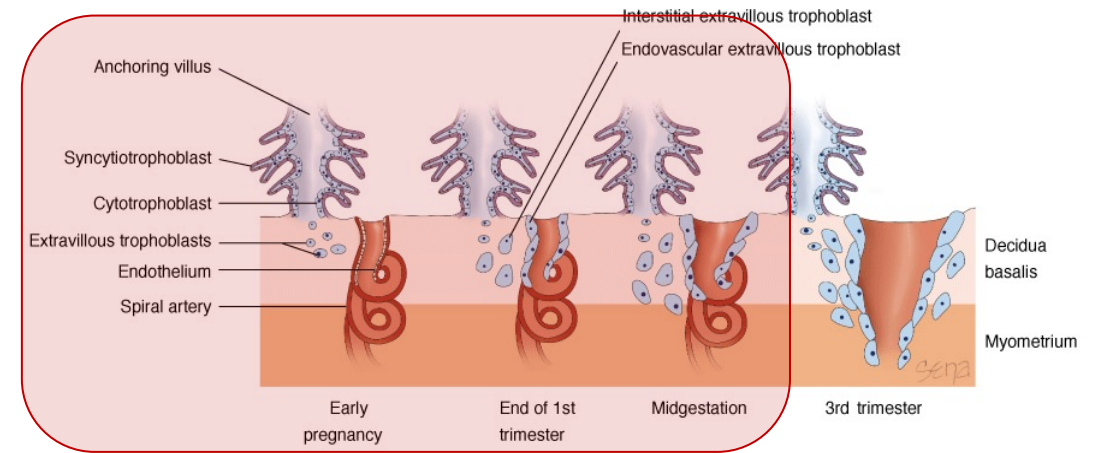


- **Threatened abortion (TAB)**
  - Vaginal bleeding (VB) within 20 weeks of gestation
  - No cervical dilation
  - Viable intrauterine pregnancy
  - Prevalence: 7%-20%

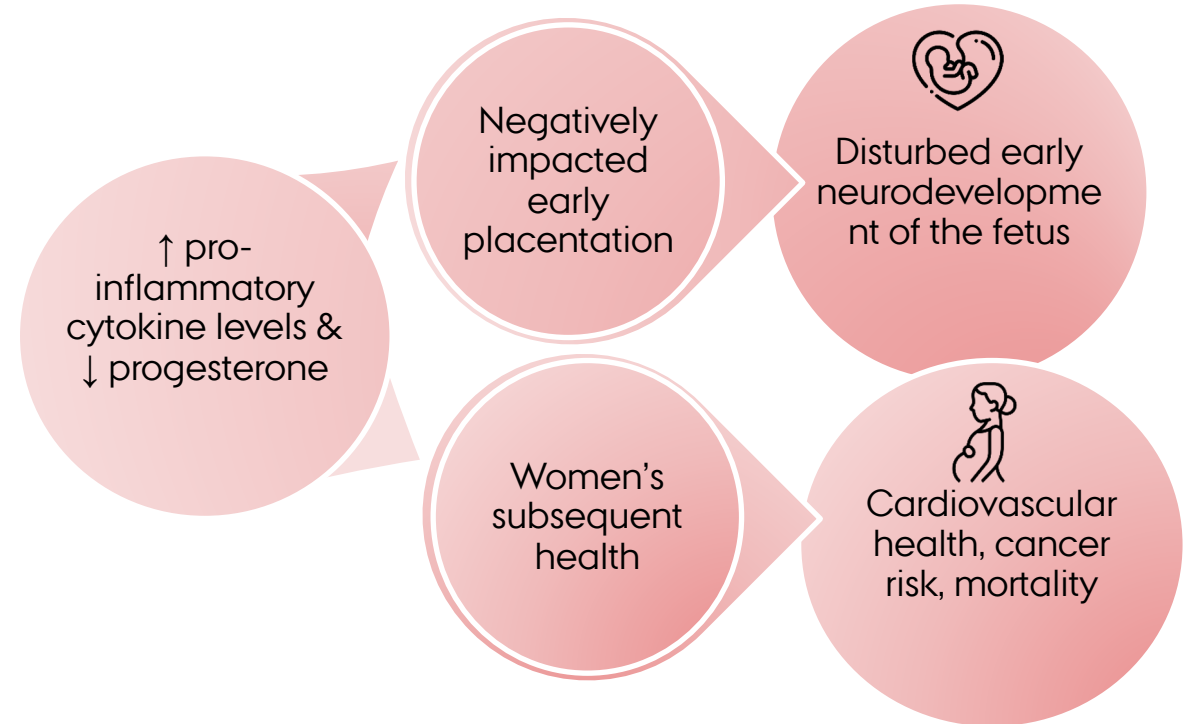


# HYPOTHESIS

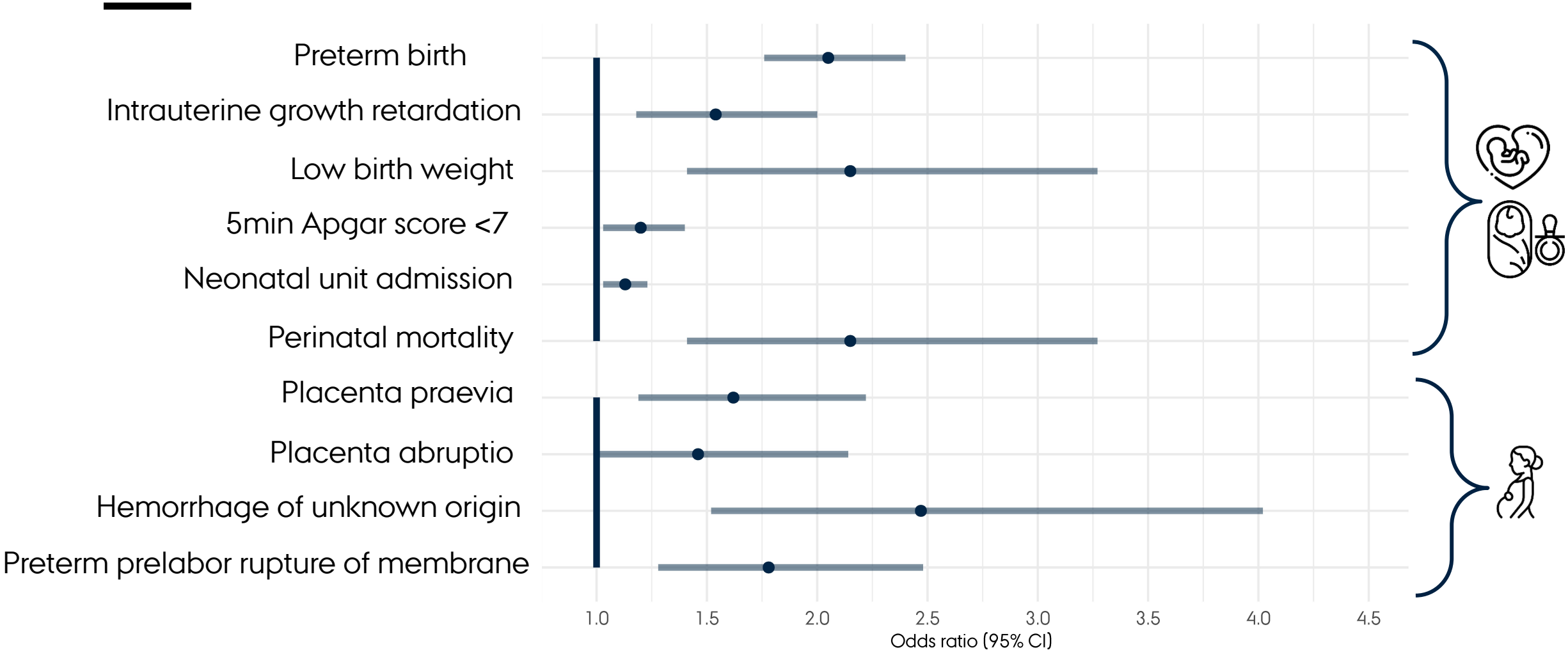
- Risk factors:
  - age  $\geq 35$  years, obesity, lack of physical exercise, stress, cigarette smoking, alcohol abuse
  - Progesterone treatment
    - PRISM RCT:  $\uparrow$  proportion of live births
  - Inflammation
    - $\uparrow$  IFN $\gamma$ ,  $\uparrow$  TNF- $\alpha$ ,  $\uparrow$  IL-6
    - Placental injury in animal studies
    - Abortogenic effect



Source: Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY: *Williams Obstetrics, 23rd Edition*: <http://www.accessmedicine.com>  
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# ADVERSE OUTCOMES AT DELIVERY



# OUTCOMES AFTER CHILDBIRTH

Autism spectrum disorder

Developmental coordination disorder

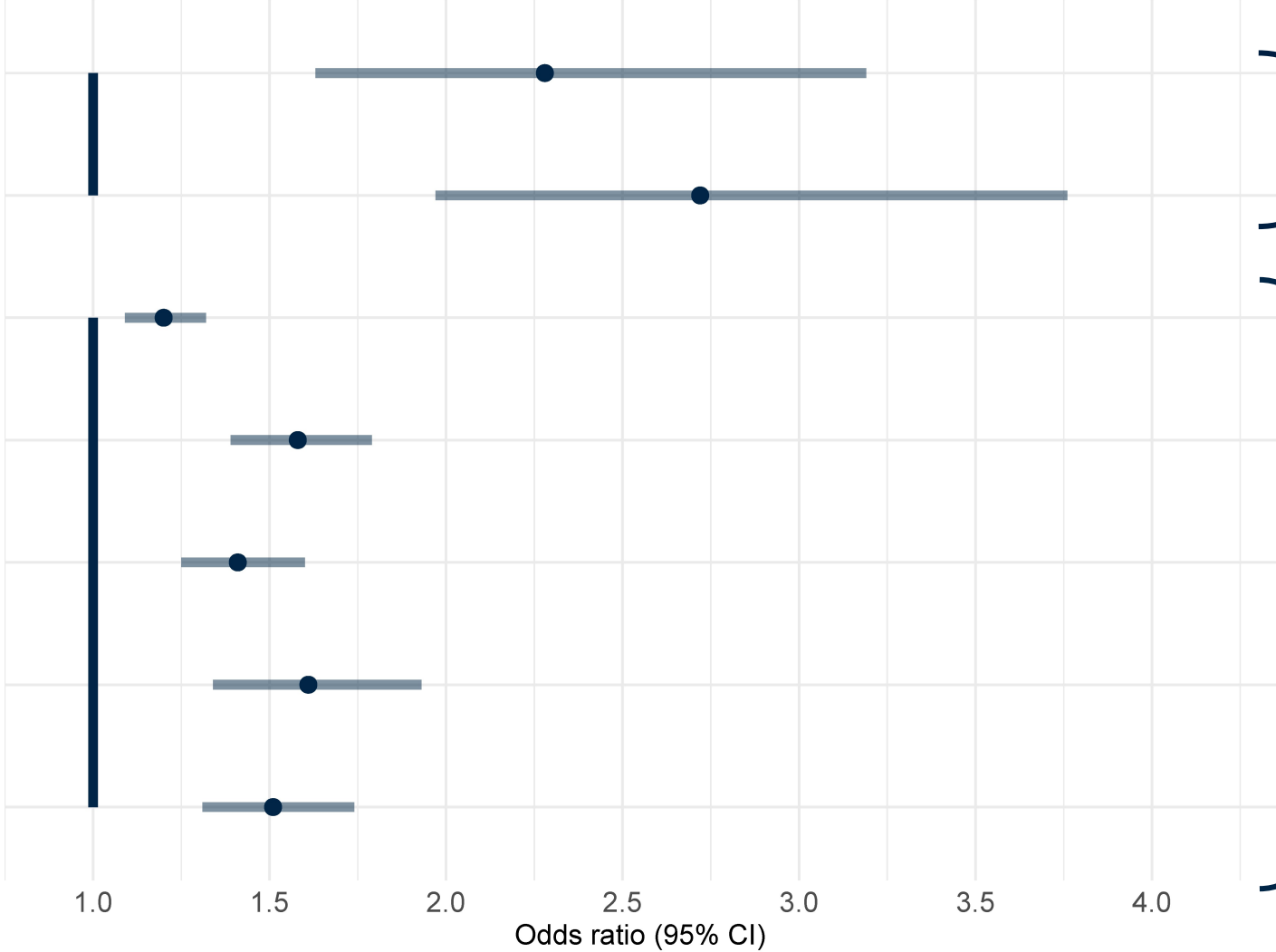
Hypertension

Ischemic heart disease

Stroke

Thrombosis

Diabetes



# RATIONALE

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- Few or no studies
- Limitations of available studies:
  - Retrospective or cross-sectional data
  - Small
  - Selective
  - Analysis limitations:
    - Residual confounding
    - “Overadjustment” for post-exposure variables
  - Design limitations
    - Time-to-event analyses not used
    - Familial confounding



## Study I



*in-utero* TAB exposure and children's risks of neurodevelopmental outcomes



## Study II

VB in pregnancy and risk of mortality in women



## Study III



VB in pregnancy and risk of cardiovascular morbidity in women



## Study IV










VB in pregnancy and subsequent risk of cancer in women



TAB, threatened abortion = VB, vaginal bleeding

# DATA SOURCES



Data source	Study I	Study II	Study III	Study IV
 Civil Registration System	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
 Medical Birth Registry	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
 National Patient Registry	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
 National Prescription Registry	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
 Education	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
 Income	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
 Registers on personal labour market affiliation	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
 Register of Causes of Death	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
 Cancer Registry	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>



# OUTCOMES

## Study I

- Epilepsy
- Cerebral palsy
- ADHD

## Study II

- All-cause mortality
- Cause-specific mortality
  - Natural causes
  - Non-natural causes

















## Study III

- Diabetes mellitus type 1
- Diabetes mellitus type 2
- CVD
  - Hypertension
  - Atrial fibrillation or flutter
  - Ischaemic heart disease
  - Myocardial infarction
  - Heart failure
  - Ischaemic stroke
  - Haemorrhagic stroke

## Study IV

- Any cancer
- Aetiological groups
- Site-specific cancers:
  - Premenopausal breast
  - Cervical
  - Ovary and fallopian tube
  - Uterine cancer

# FEATURES OF THE STUDIES

	Study I	Study II	Study III	Study IV
Main study period(s)	1979+; 1995+	1979+	1994+	1995+
Cohort study design				
Sibling comparisons				
Unit of observation				
Measure of association	Hazard ratio	Hazard ratio	Hazard ratio	Hazard ratio
Cox proportional hazards regression	Conventional multivariable models; clustered by family id, robust SE	IPT-weighted models; bootstrapping	IPT-weighted models; bootstrapping	Conventional multivariable models; robust SE
Competing risks				

# STUDY I DESIGN



Last menstrual period date  
(eligibility start)

20 week of  
gestation

Delivery Date (Time zero; eligibility end)

Exposure Assessment  
Window  
Days [LMP, 140 days]



# STUDY I DESIGN



Last menstrual period date  
(eligibility start)

20 week of  
gestation

Delivery Date (Time zero; eligibility end)

Exposure Assessment  
Window  
Days [LMP, 140 days]



**Covariables Assessment Window  
(Baseline morbidities):**

Maternal somatic, neurologic, psychiatric conditions & paternal age, psychiatric co-morbidities; paternal prescriptions of antiepileptics or ADHD medication

Days [-Inf, LMP-1]

**Covariables Assessment Window  
(Baseline medication and  
healthcare utilization):**  
Days [-365, LMP-1]

**SES factors:  
Year before the  
Delivery Year**

Time

# STUDY I DESIGN



Last menstrual period date  
(eligibility start)

20 week of  
gestation

Delivery Date (Time zero; eligibility end)

Exposure Assessment  
Window  
Days [LMP, 140 days]

**EXCL**  
CPR number duplicates, non-singleton birth, born  
outside of the study period; unknown gestational  
age; stillbirth  
Days [0, 0]

**Covariables Assessment Window  
(Baseline morbidities):**  
Maternal somatic, neurologic, psychiatric conditions &  
paternal age, psychiatric co-morbidities; paternal prescriptions  
of antiepileptics or ADHD medication  
Days [-Inf, LMP-1]

**Covariables Assessment Window  
(Baseline medication and  
healthcare utilization):**  
Days [-365, LMP-1]

**SES factors:  
Year before the  
Delivery Year**

**Covariate Assessment Date  
(Maternal and paternal age at childbirth,  
newborns' sex, birth year, birth order)**  
Days [0, 0]

Time

# STUDY I DESIGN



Last menstrual period date  
(eligibility start)

20 week of  
gestation

Delivery Date (Time zero; eligibility end)

Exposure Assessment  
Window  
Days [LMP, 140 days]

**EXCL**  
CPR number duplicates, non-singleton birth, born  
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Days [0, 0]

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Maternal somatic, neurologic, psychiatric conditions &  
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of antiepileptics or ADHD medication  
Days [-Inf, LMP-1]

**Covariate Assessment Date**  
(Maternal and paternal age at childbirth,  
newborns' sex, birth year, birth order)  
Days [0, 0]

**Covariables Assessment Window  
(Baseline medication and  
healthcare utilization):**  
Days [-365, LMP-1]

**SES factors:**  
Year before the  
Delivery Year

**Follow up Window**  
Days [Delivery; Stop<sup>b</sup>]

Time

Study end:  
31 December 2016

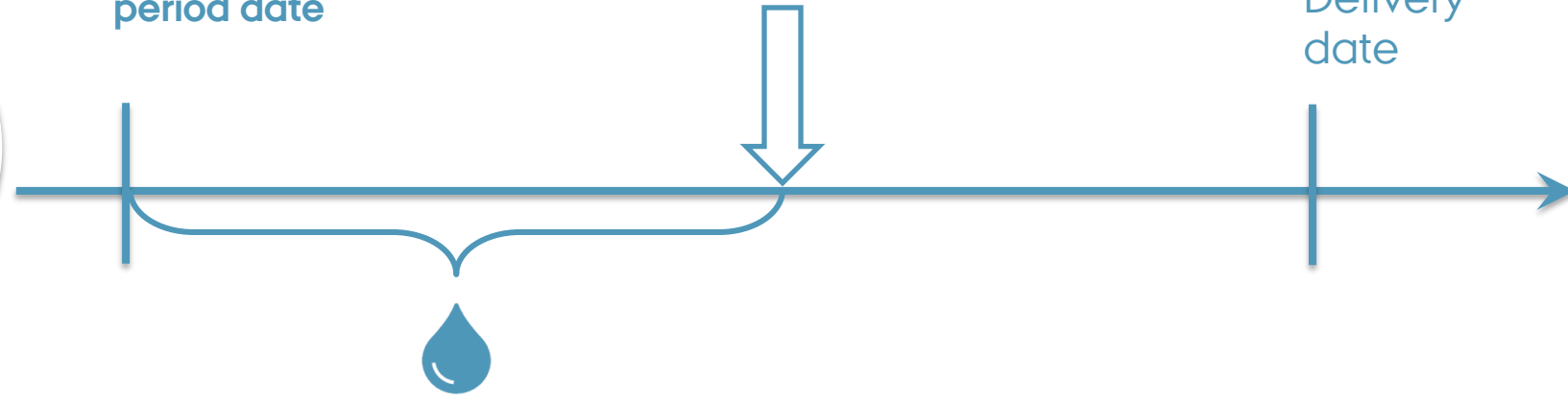
# STUDIES II-IV



Last menstrual period date

20th week gestation

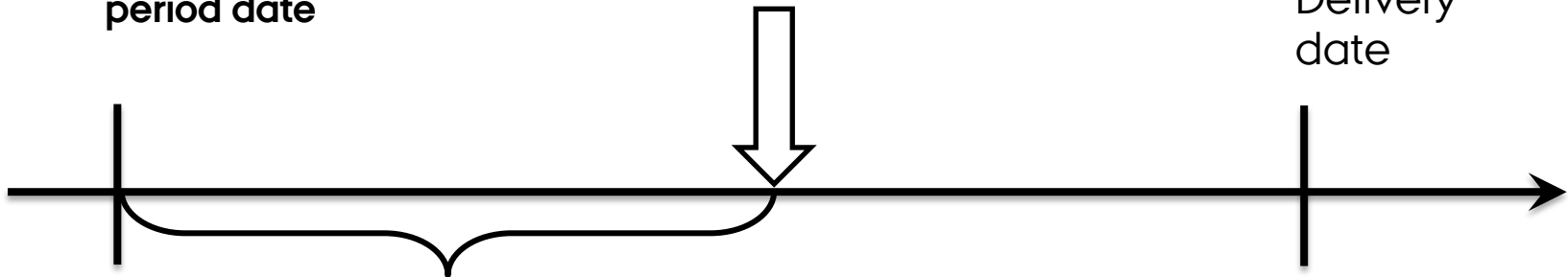
Delivery date



Last menstrual period date

20th week gestation

Delivery date



# STUDIES II-IV



Pregnancy  
end date



 termination



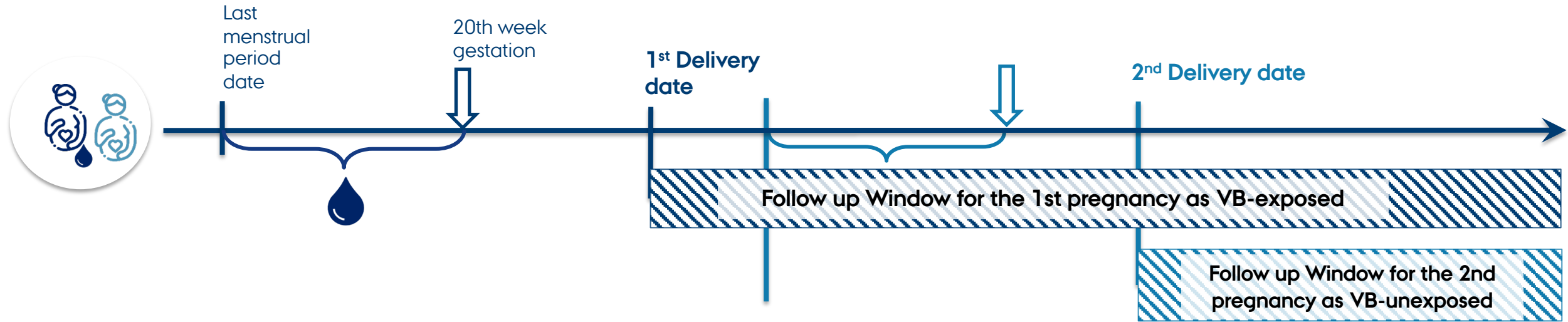
Pregnancy  
end date



 miscarriage



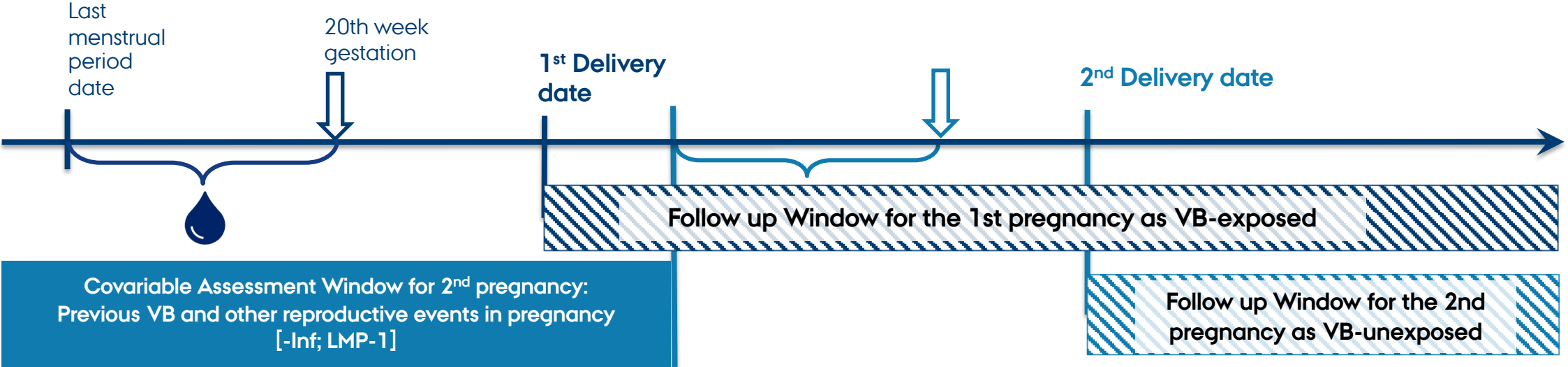
# ALL VS 1<sup>ST</sup> PREGNANCY OF A WOMAN



 1<sup>st</sup> pregnancy ending in a delivery

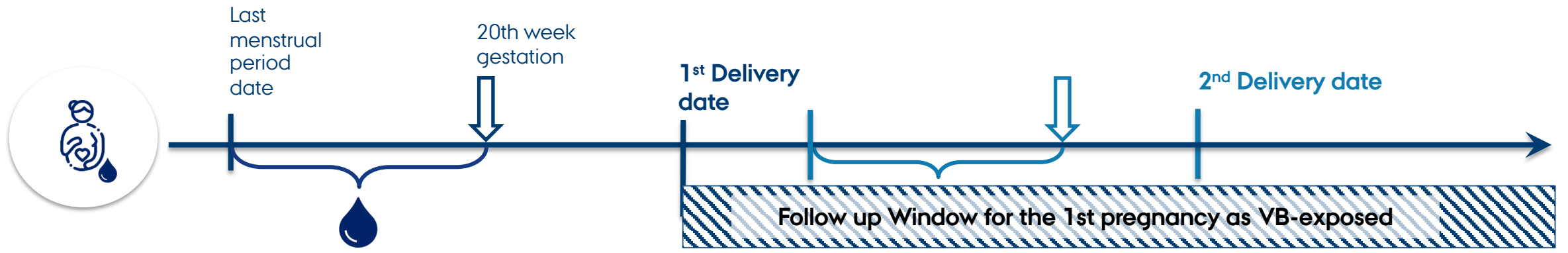
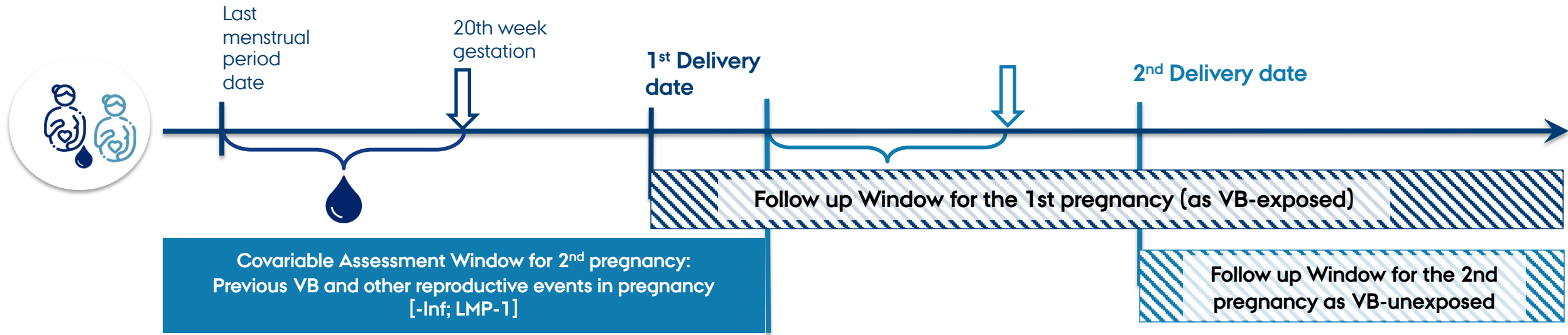
 2<sup>nd</sup> pregnancy ending in a delivery

# ALL VS 1<sup>ST</sup> PREGNANCY OF A WOMAN



1<sup>st</sup> pregnancy ending in a delivery 2<sup>nd</sup> pregnancy ending in a delivery

# ALL VS 1<sup>ST</sup> PREGNANCY OF A WOMAN



 1<sup>st</sup> pregnancy ending in a delivery
  2<sup>nd</sup> pregnancy ending in a delivery

# STUDY POPULATION: STUDY I



## Study I: 1979-2010



No.

Live born singletons	<b>59,134</b>	1,805,087
Paternal siblings	<b>39,573</b>	39,573
Maternal siblings	<b>42,510</b>	42,510
Full siblings	<b>35,161</b>	35,161

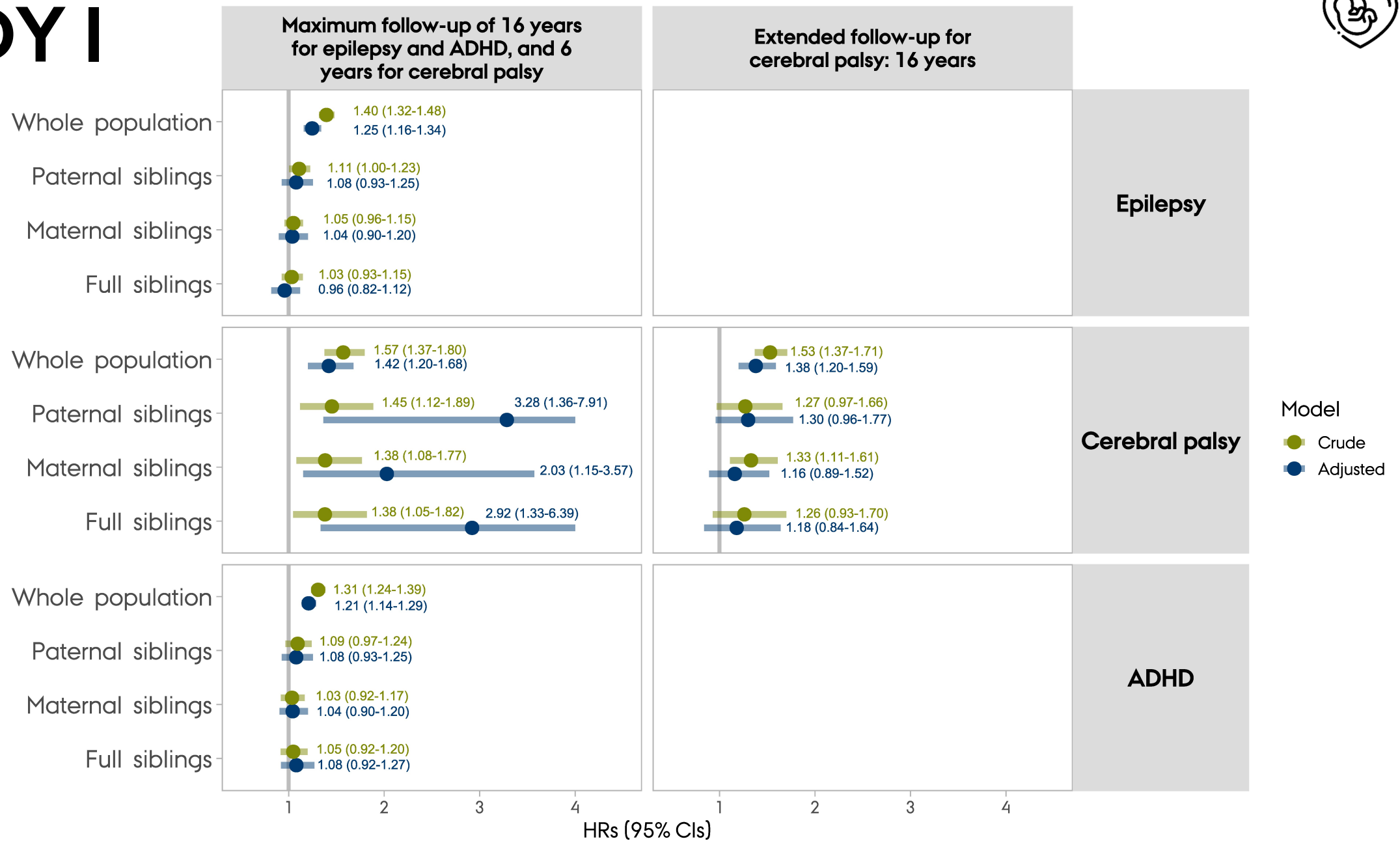
## Study I: 1995-2010



No.

Live born singletons	<b>28,428</b>	955,066
Paternal siblings	<b>17,497</b>	17,497
Maternal siblings	<b>17,818</b>	17,818
Full siblings	<b>15,876</b>	15,876

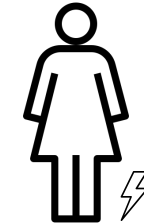
# STUDY I



# STUDY POPULATIONS: STUDIES II-IV



1979-2017



			No.	
All pregnancies of a woman	<b>70,835</b>	2,236,359	589,699	265,940
Distinct women	<b>66,881</b>	1,198,206	424,834	225,103
1 <sup>st</sup> pregnancy of a woman	<b>19,631</b>	841,096	251,450	94,086

The same woman could be included in several cohorts with her every next pregnancy when she met all inclusion criteria  
 No. 1<sup>st</sup> identifiable pregnancies = No. distinct women. Cohort membership of the 1<sup>st</sup> identifiable pregnancy is mutually exclusive

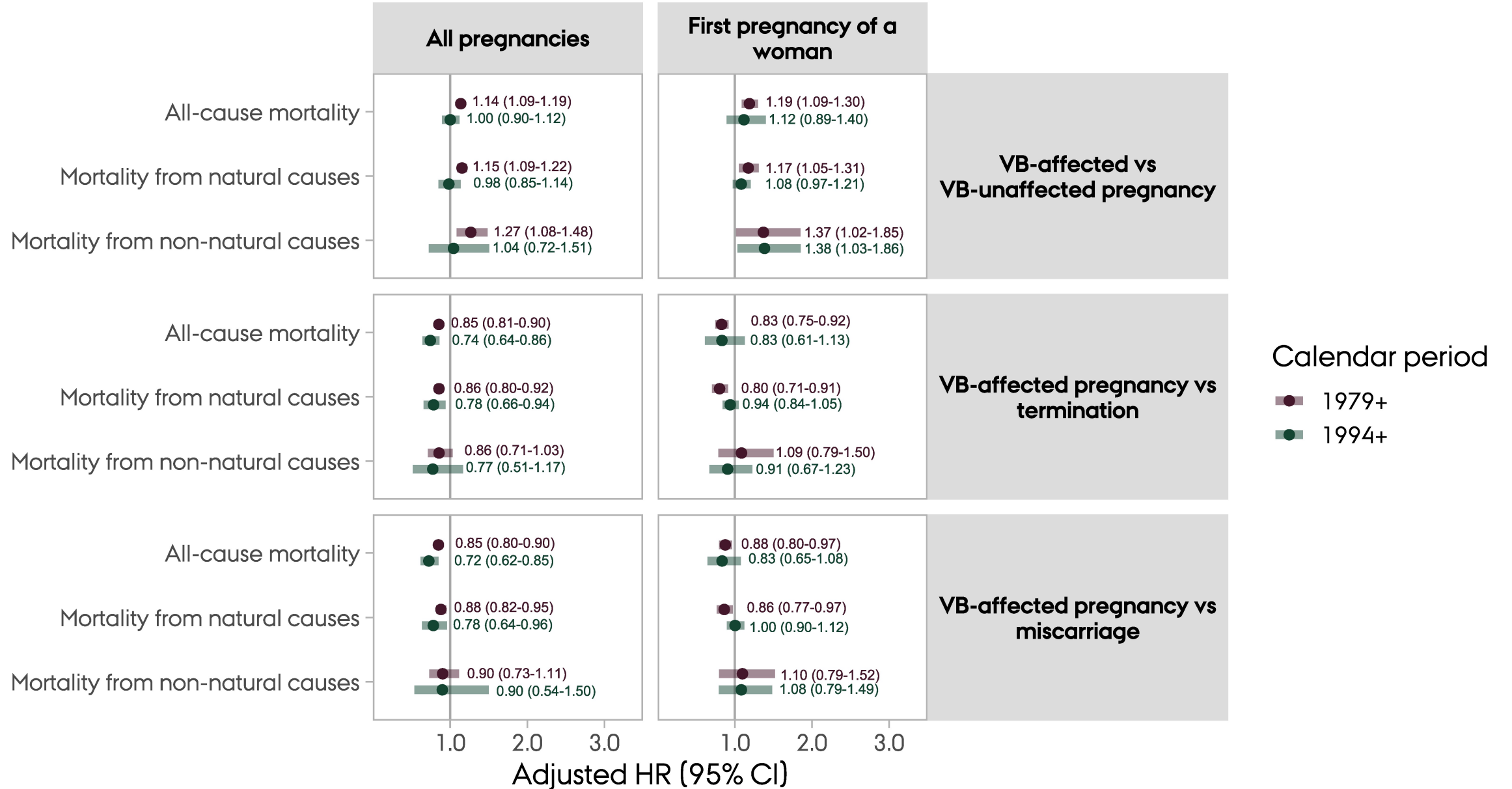


termination

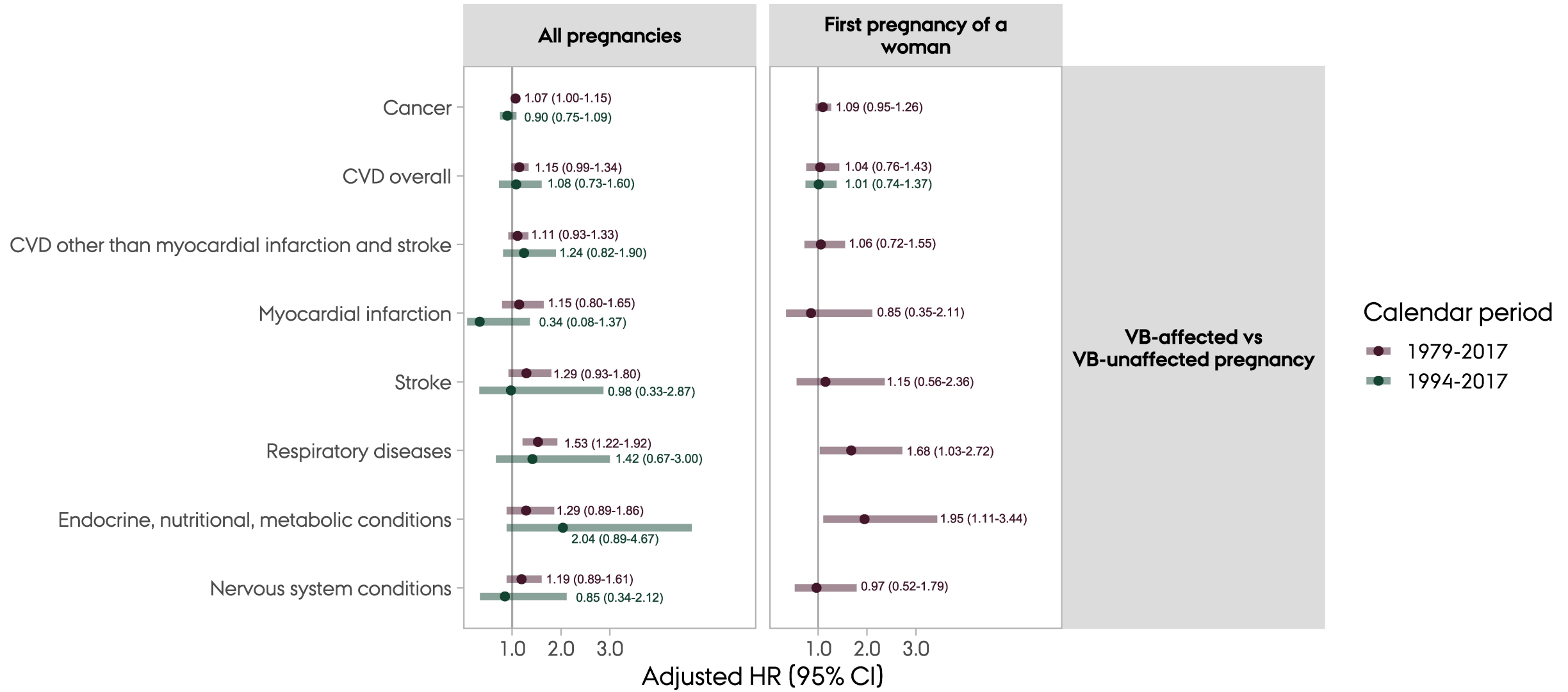


miscarriage

# STUDY II: MORTALITY CAUSES

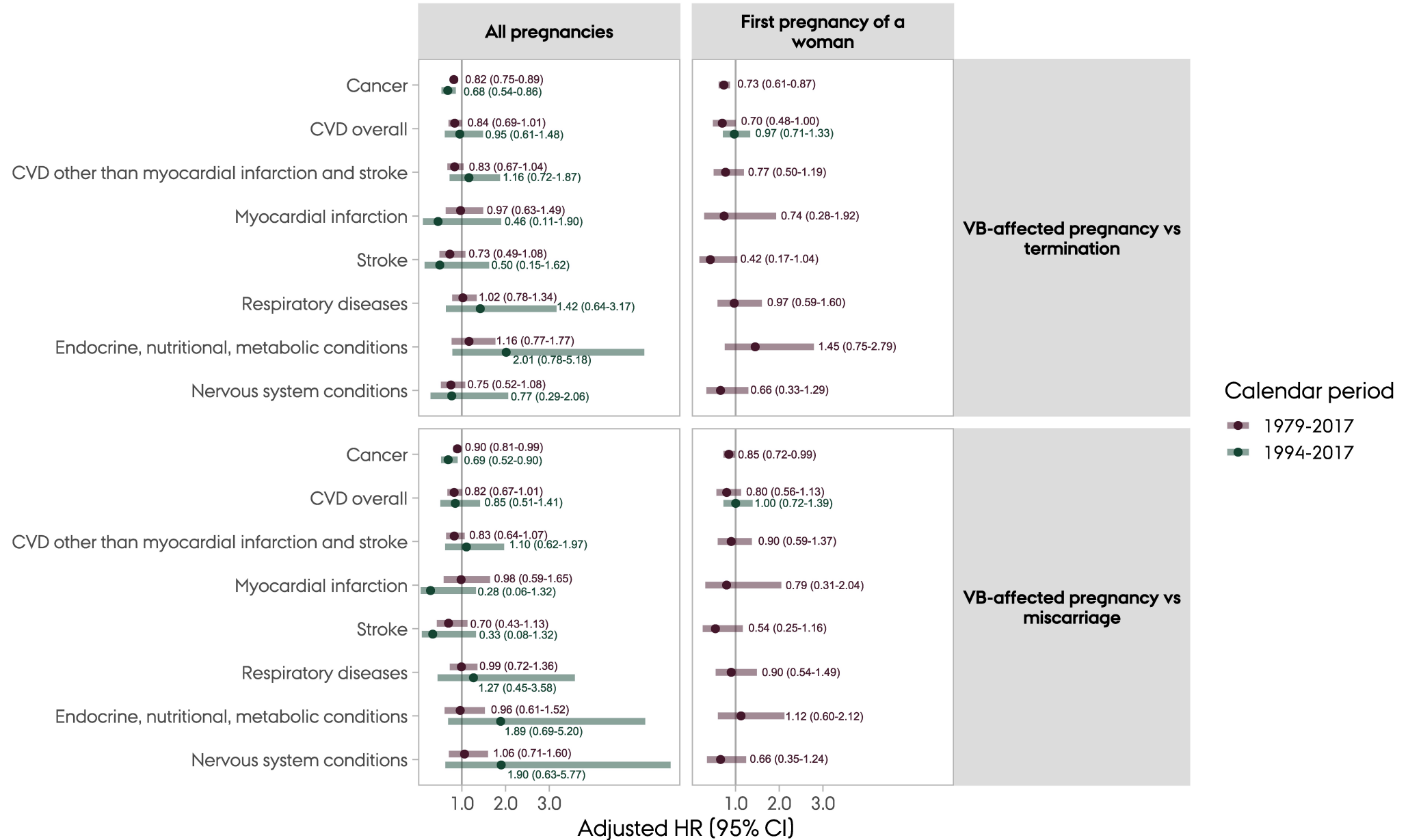


# STUDY II: NATURAL CAUSES MORTALITY

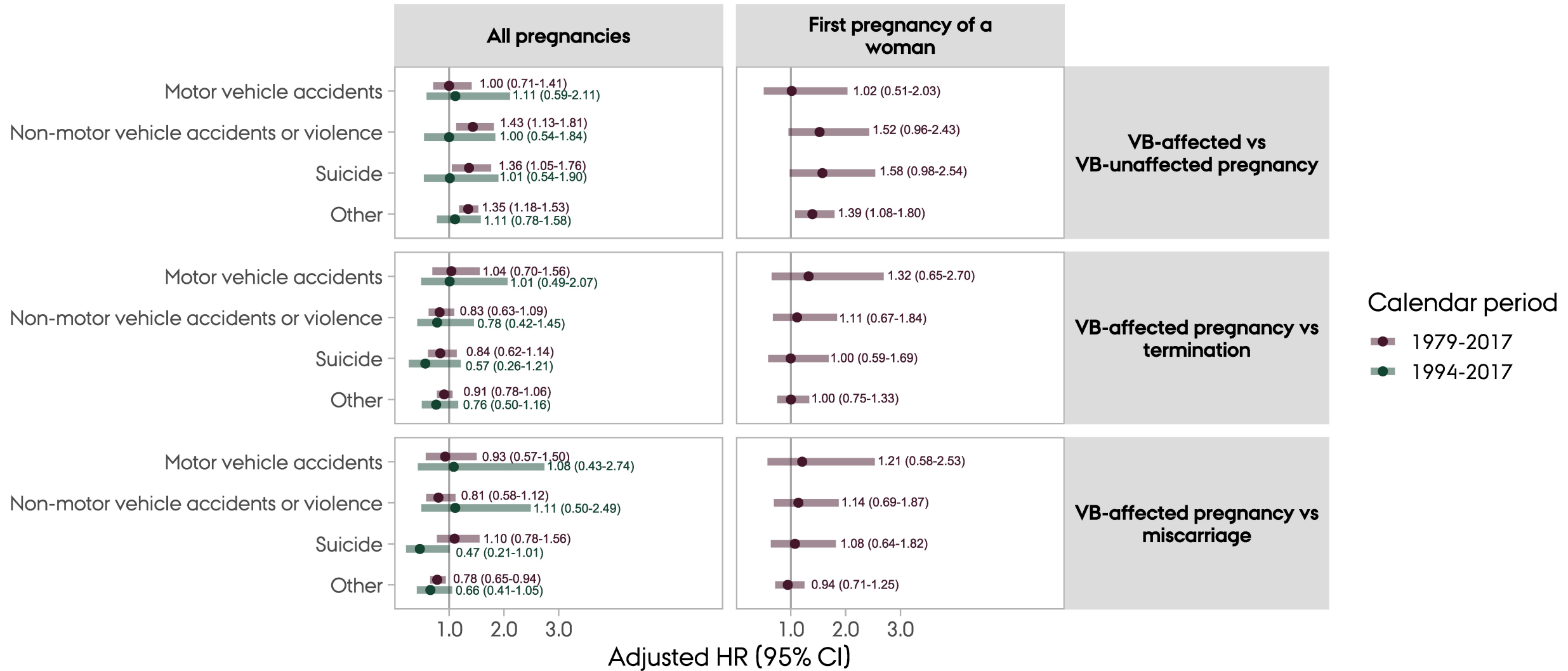




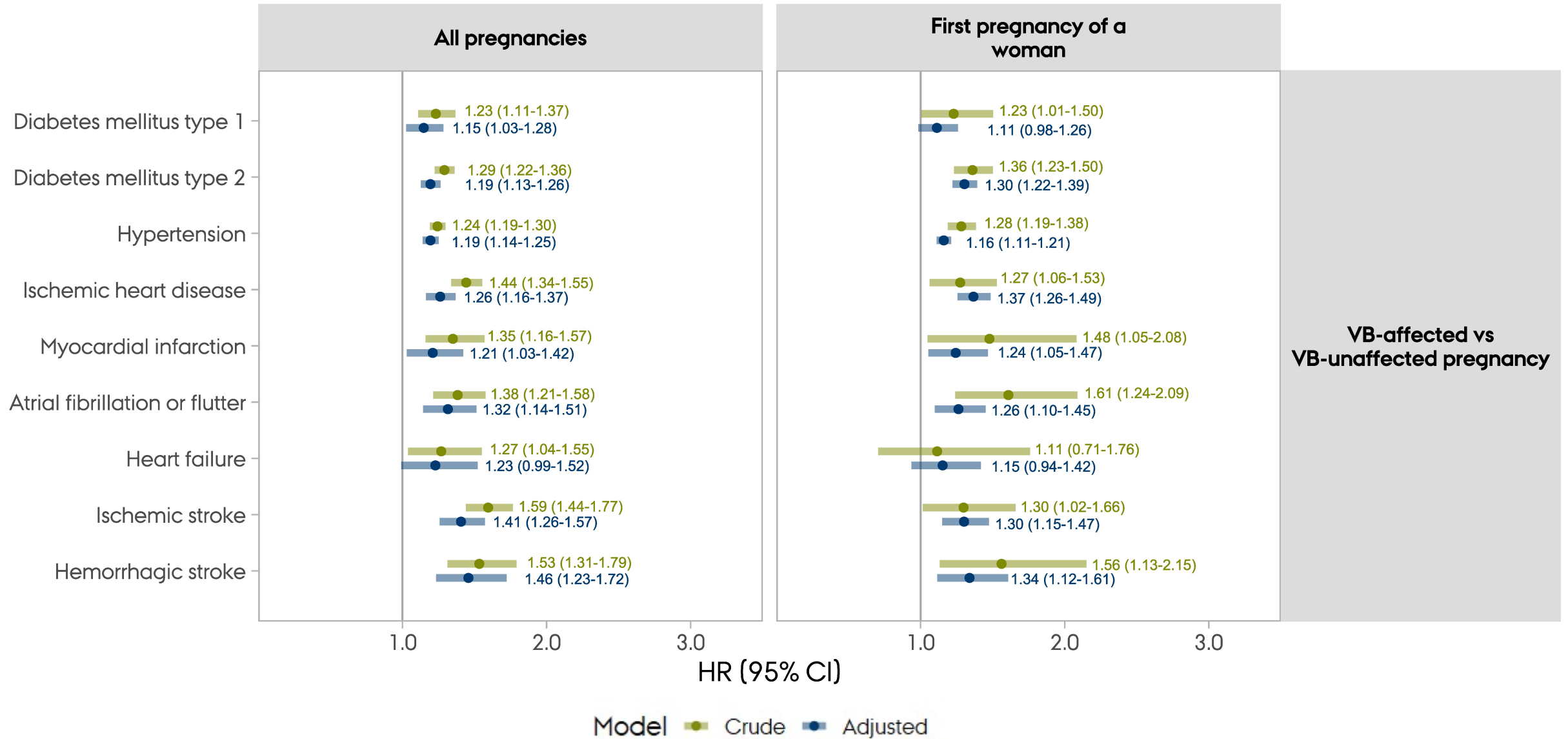
# STUDY II: NATURAL CAUSES MORTALITY



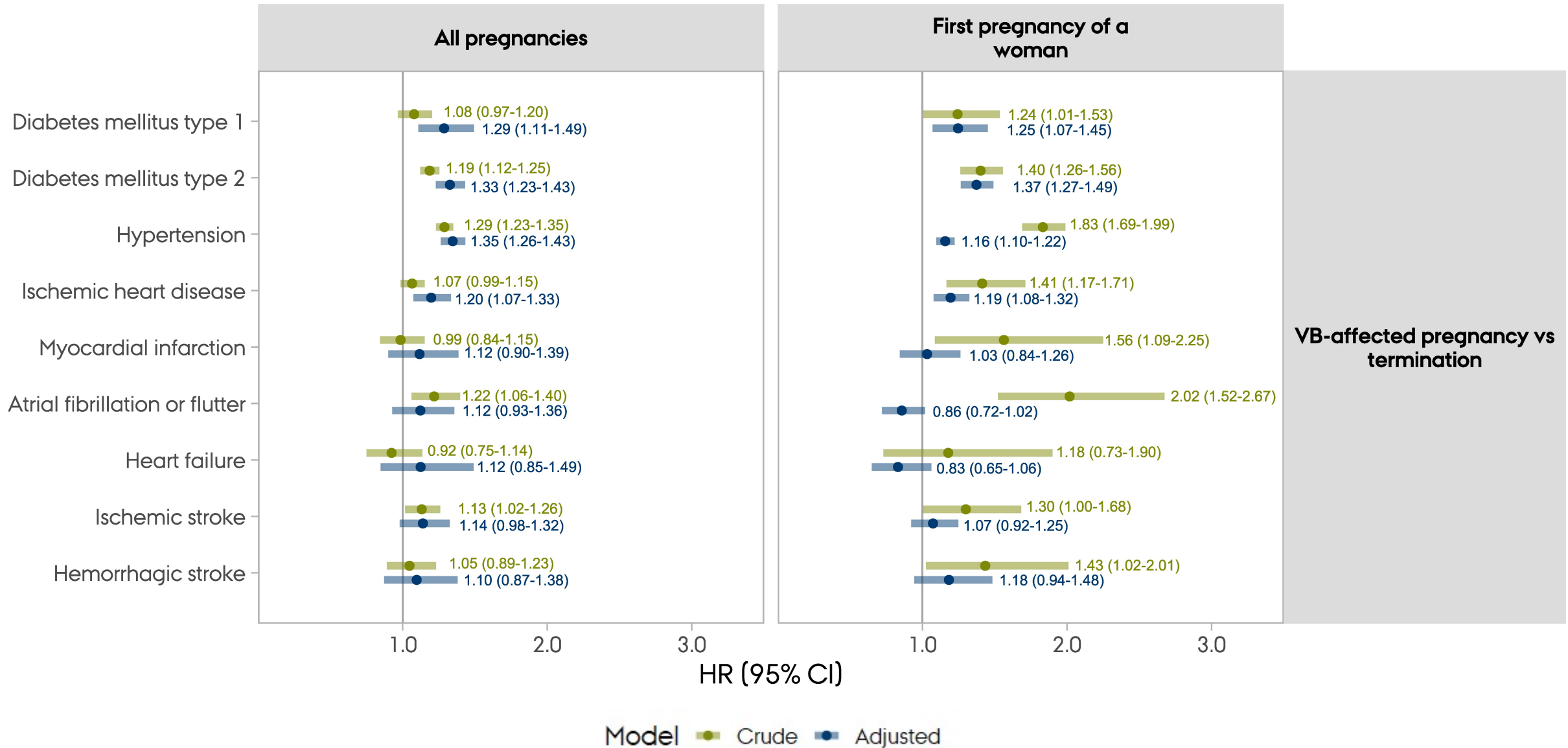
# STUDY II: NON-NATURAL CAUSES MORTALITY



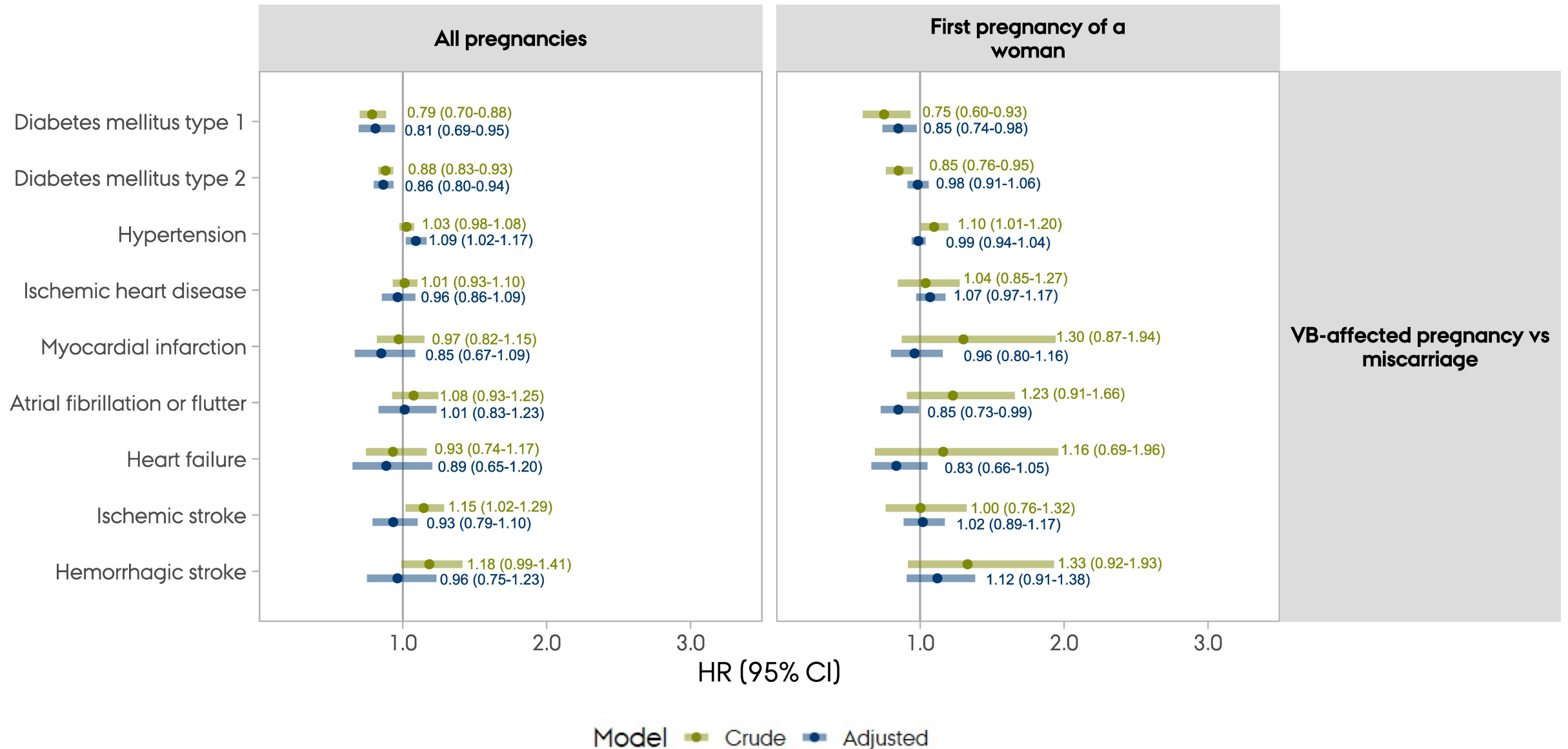
# STUDY III: DIABETES AND CVD OUTCOMES



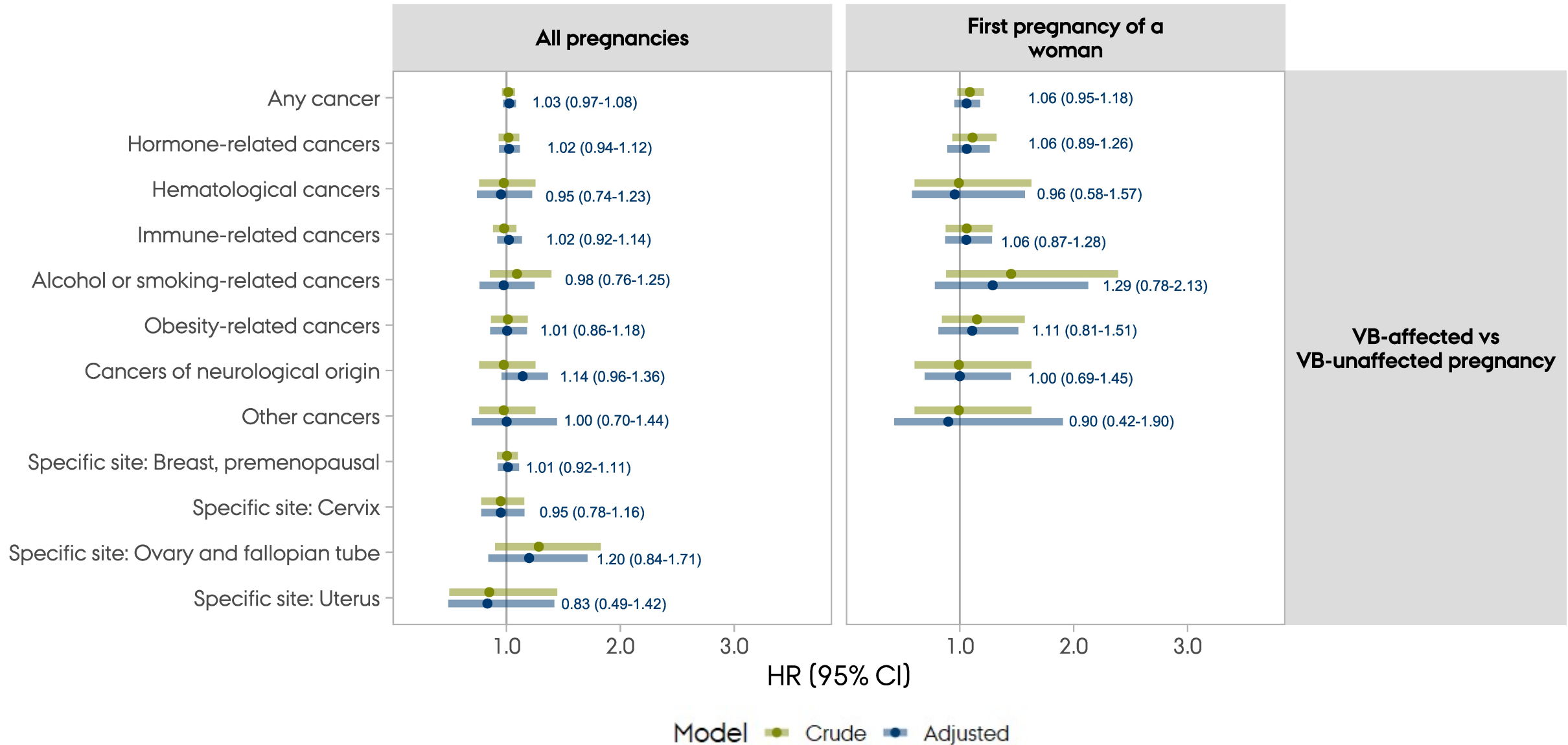
# STUDY III: DIABETES AND CVD OUTCOMES



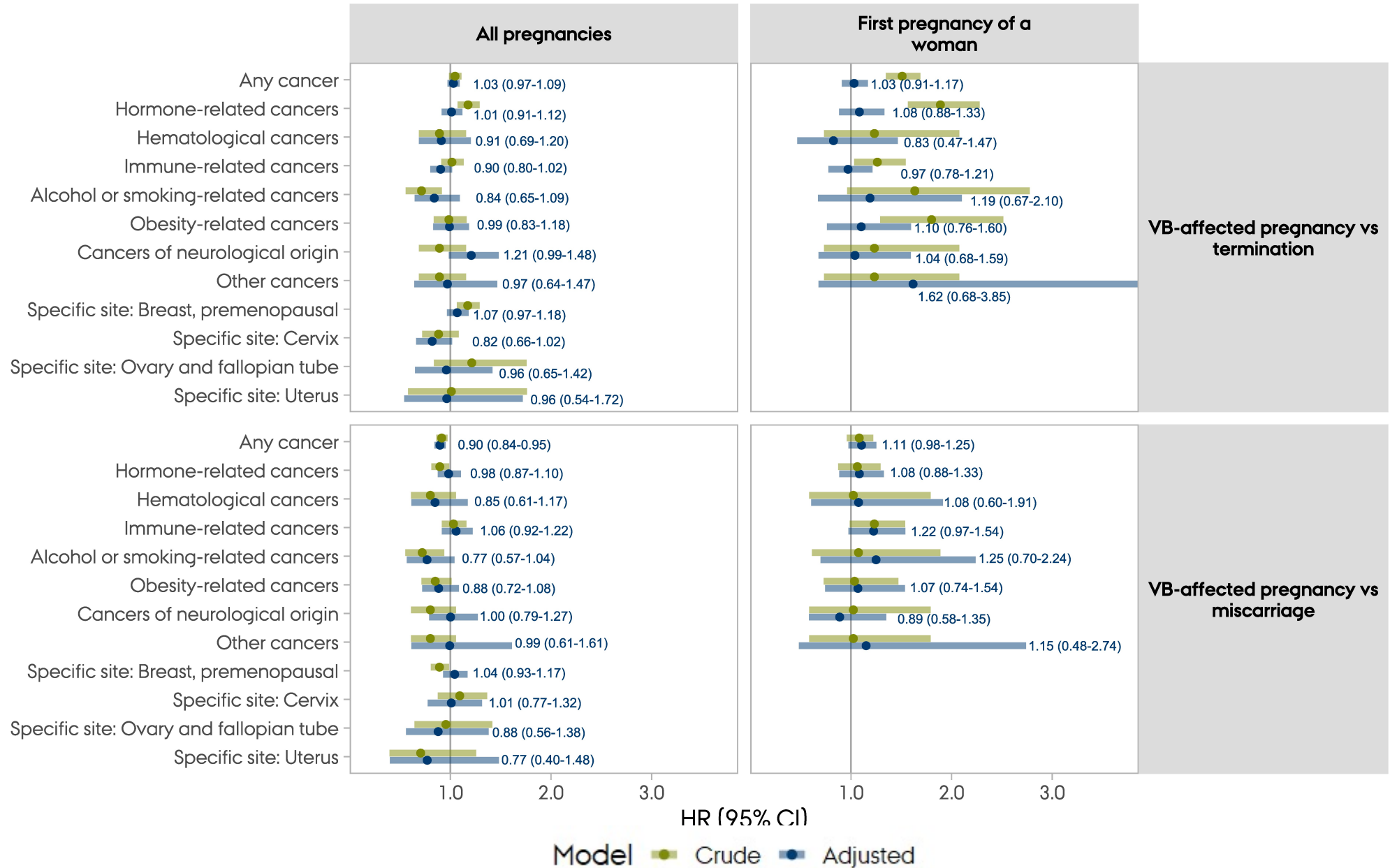
# STUDY III: DIABETES AND CVD OUTCOMES



# STUDY IV: CANCER



# STUDY IV: CANCER



# STUDY I

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## Study I

## Take home message



- On the relative scale, *in-utero* TAB exposure was not associated with children's risks of epilepsy and ADHD, but was associated with cerebral palsy.
- Small absolute risk of cerebral palsy for both *in-utero* TAB-exposed and TAB-unexposed children.
- **Substantial attenuation of the associations in the sibling analyses** suggests that the associations in the full population may be explained by time-invariant **family-shared confounding**.





# STUDY II

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Study II

Outcome

Take home message



- No strong evidence of increased risk of mortality in women following VB-affected vs VB-unaffected pregnancy ending in childbirth.
- Comparisons of VB-affected pregnancies with terminations or miscarriages showed slightly reduced risks of mortality.
- Results of all pregnancies analyses are consistent with the results of analyses of 1<sup>st</sup> pregnancy of a woman.

# STUDY III

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Study III

Outcome

Take home message



- VB in pregnancy is associated with 1.2 to 1.5-fold increased risks of diabetes type 1 and 2 and cardiovascular diseases in women.
- Comparisons of VB-affected pregnancies with terminations suggested up to 1.3-fold increased risks of diabetes type 1 and 2, hypertension and ischemic heart disease.
- Comparisons with miscarriages resulted in estimates close to the null value.
- Results of all pregnancies analyses are consistent with the results of analyses of 1<sup>st</sup> pregnancy of a woman.

# STUDY IV

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Study IV

Outcome

Take home message



- No strong evidence of increased risk of any and site-specific cancers in women.
- Results of all pregnancies analyses are consistent with the results of analyses of 1<sup>st</sup> pregnancy of a woman.



# STRENGTHS

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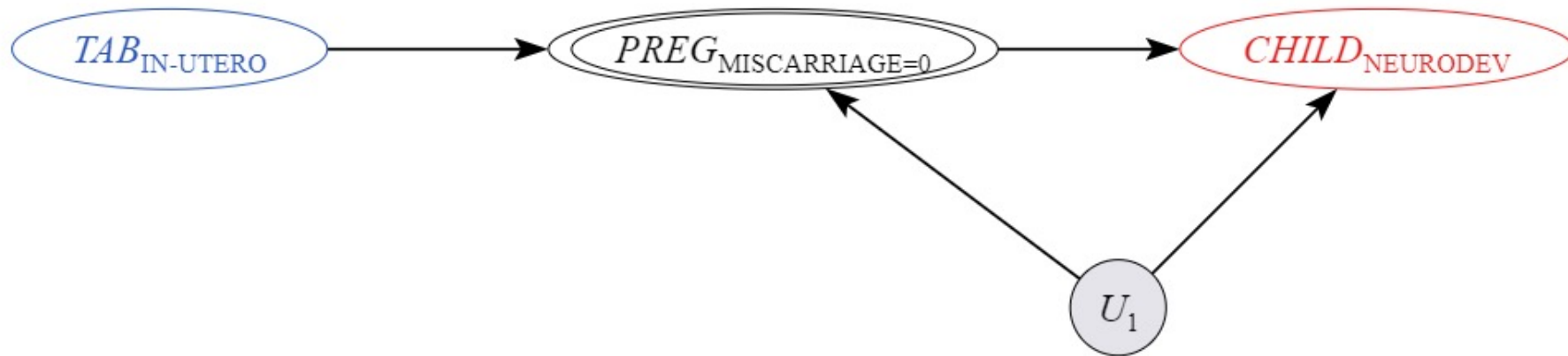


- Control of familial confounding for investigation of children's outcomes
- Use of appropriate time-to-event design
- Validated outcomes
- Closing the gap in the literature on the long-term sequelae of a common “mild” pregnancy complication

# SELECTION BIAS



- Attrition before birth: “live-birth bias”



# INFORMATION BIAS

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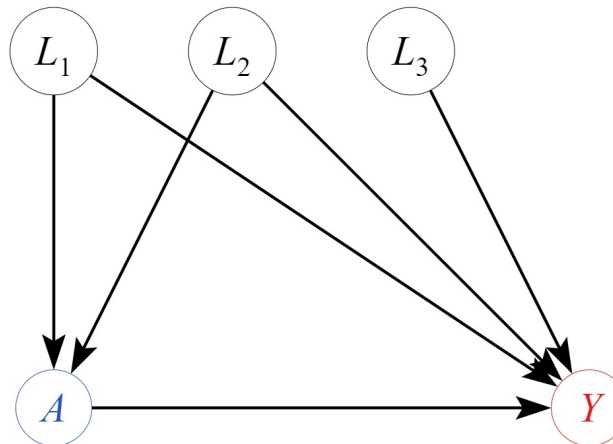


- Exposure misclassification
  - Threatened abortion coding: not validated
    - Spontaneous abortion: PPV is 98%
  - Prevalence of 3% in the DNPR vs 19% in questionnaire based Danish study
- Outcome misclassification
  - Cerebral palsy
  - Cause-specific mortality

# CONFOUNDING



- Exchangeability between exposed and unexposed
  - Untestable assumption
- Residual:
  - Possibly mismeasured: socioeconomic position, smoking, alcohol abuse, adiposity
- Unmeasured:
  - Lifestyle determinants beyond smoking and alcohol abuse, low grade inflammation, fertility



# OTHER CONSIDERATIONS

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- Inherent selection bias of hazard ratios
  - Conditional probability of experiencing the endpoint within the next time point given that the event has not yet occurred
- Causal assumptions:
  - Exchangeability: no residual and unmeasured confounding
  - Positivity
  - **Consistency: VB is not a “well-defined” exposure**
- External validity: Nordic countries
- Longitudinal (cumulative/total) effect of having VB and/or miscarriage in multiple successive pregnancies not investigated



# CONCLUSIONS

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- Children TAB-affected *in utero* had a greater relative risk of cerebral palsy, but not of epilepsy or ADHD.
- VB-affected pregnancy was associated with a 1.2-fold increased risk of diabetes type 1 and type 2 and up to a 1.5-fold increased risk of multiple cardiovascular conditions, but not with increased risks of cancer and mortality in women.
- This work contributes to the knowledge on women's reproductive events and different aspects of their own and their children's later health.

- Assessment Committee for careful evaluation of my PhD thesis
  - Bodil Hammer Bech, MD, PhD, Associate Professor (Chair)
  - Tina Kold Jensen, MD, PhD, Professor
  - Rolv Arnold Skjærven, PhD, Professor
- For endless support, superb supervision, and possibility to work on pharmacoepidemiologic studies alongside the PhD project
  - Vera Ehrenstein, Professor, DSc
  - Erzsébet Horváth-Puhó, Associate professor, PhD
  - Henrik Toft Sørensen, Professor, DMSc
- Onyebuchi A. Arah, Professor, Skou-professor and my host at UCLA
- Jan P. Vandenbroucke, Professor
- PhD group
- Administration team and especially to Sascha and Helle
- Everyone at DCE

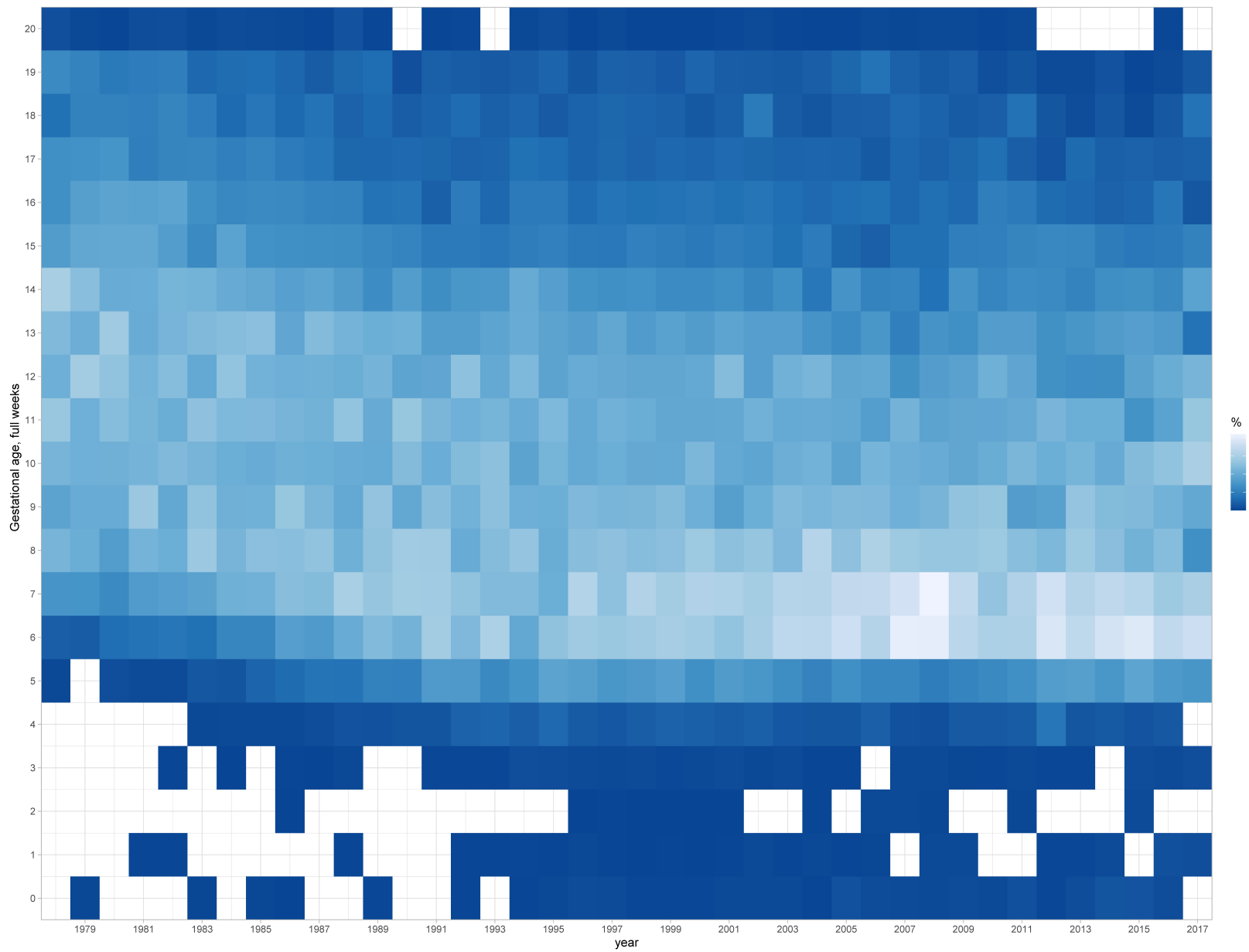


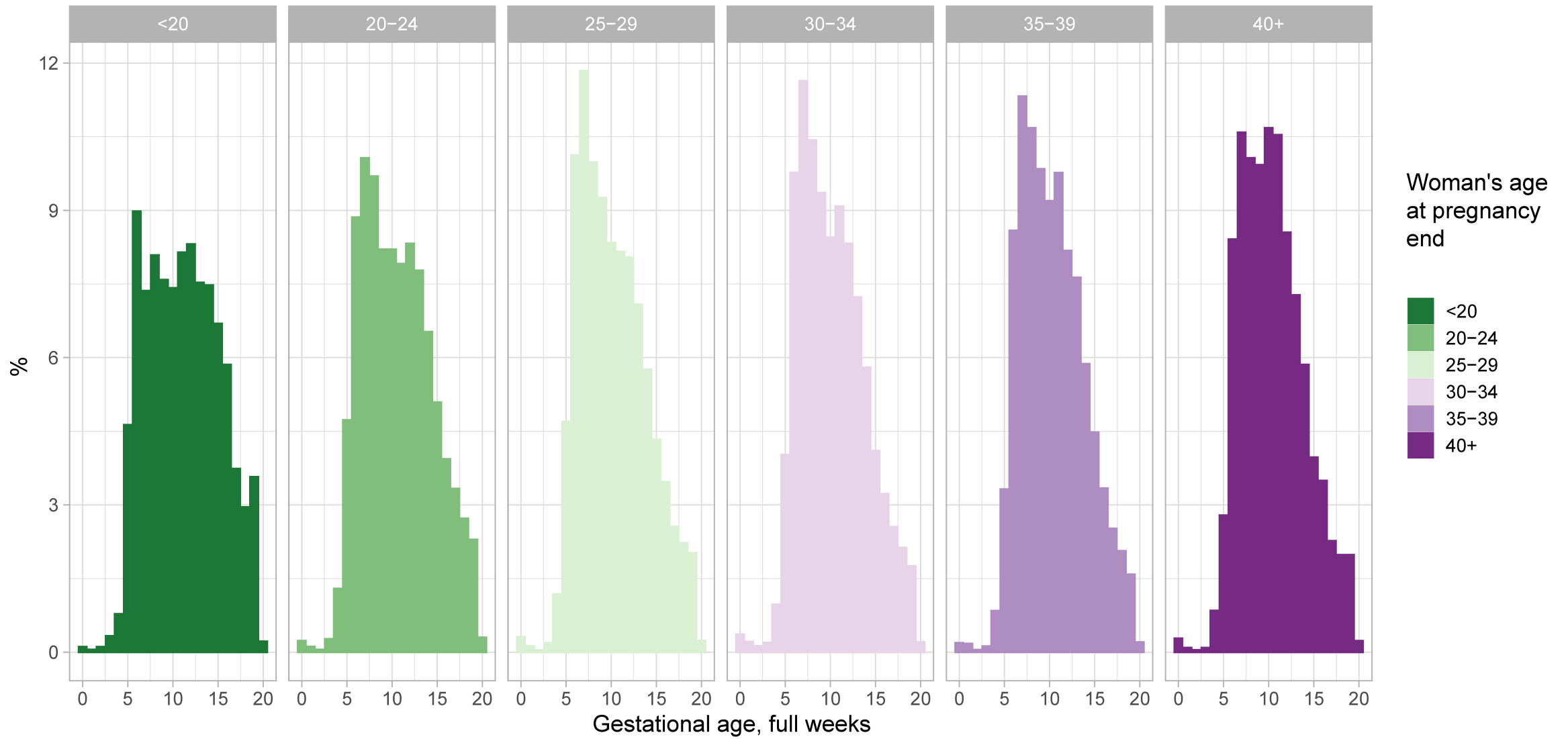


AARHUS  
UNIVERSITY

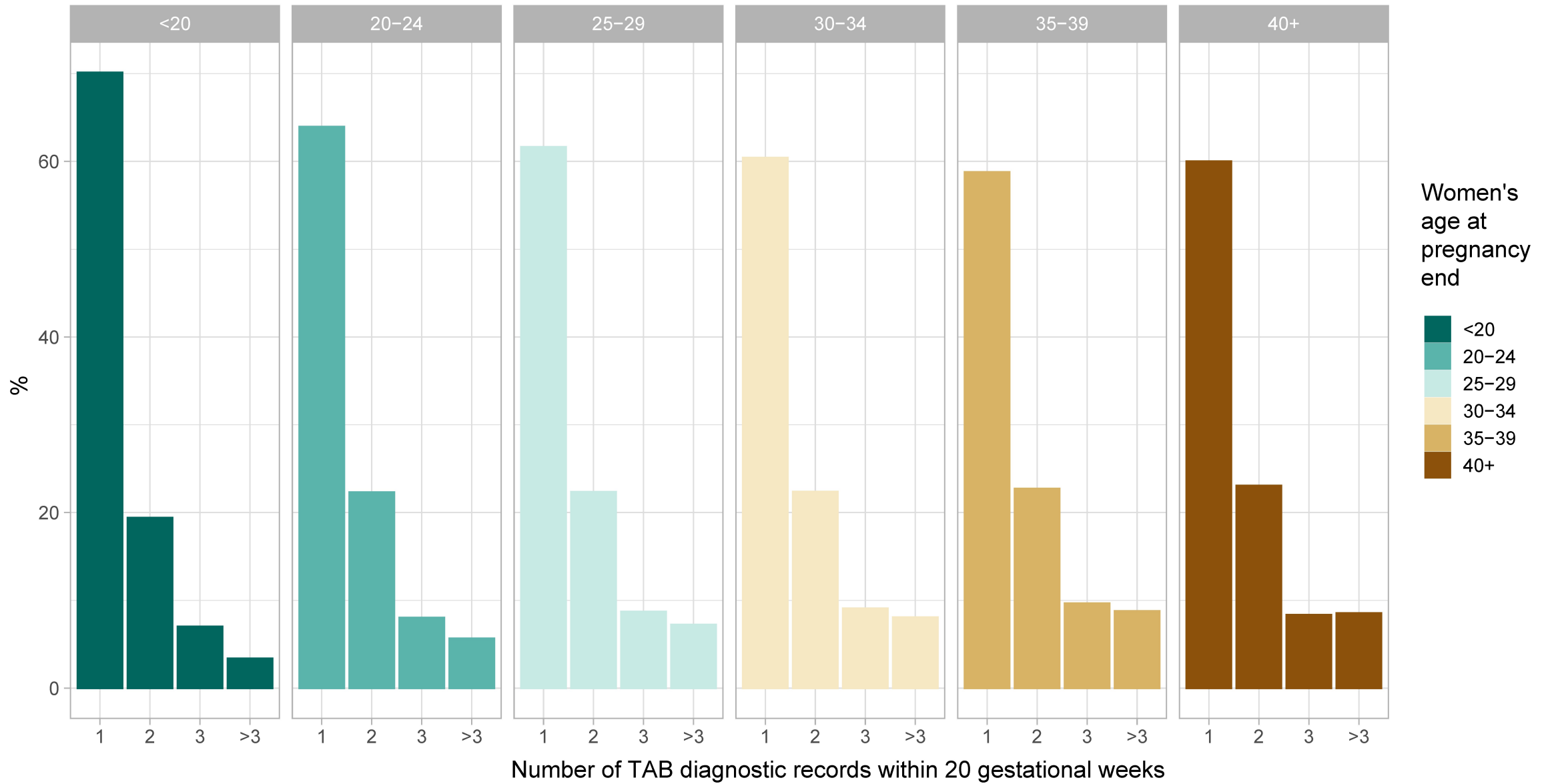


# ADDITIONAL SLIDES

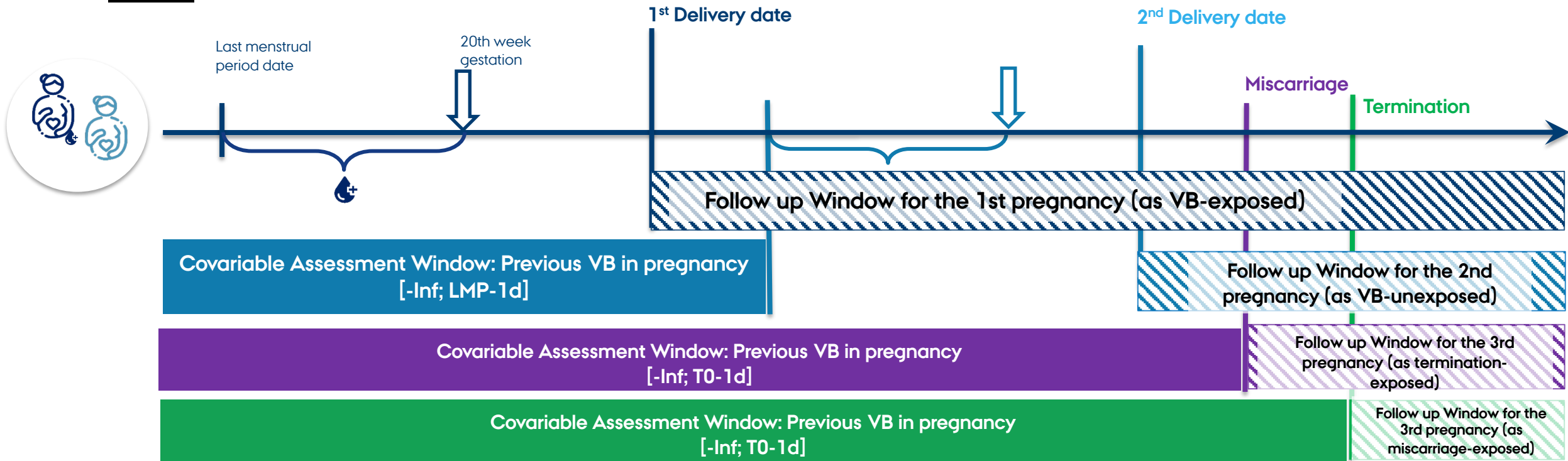




The plot is based on the data with repeated TAB diagnostic records within 20 gestational weeks of the same pregnancy

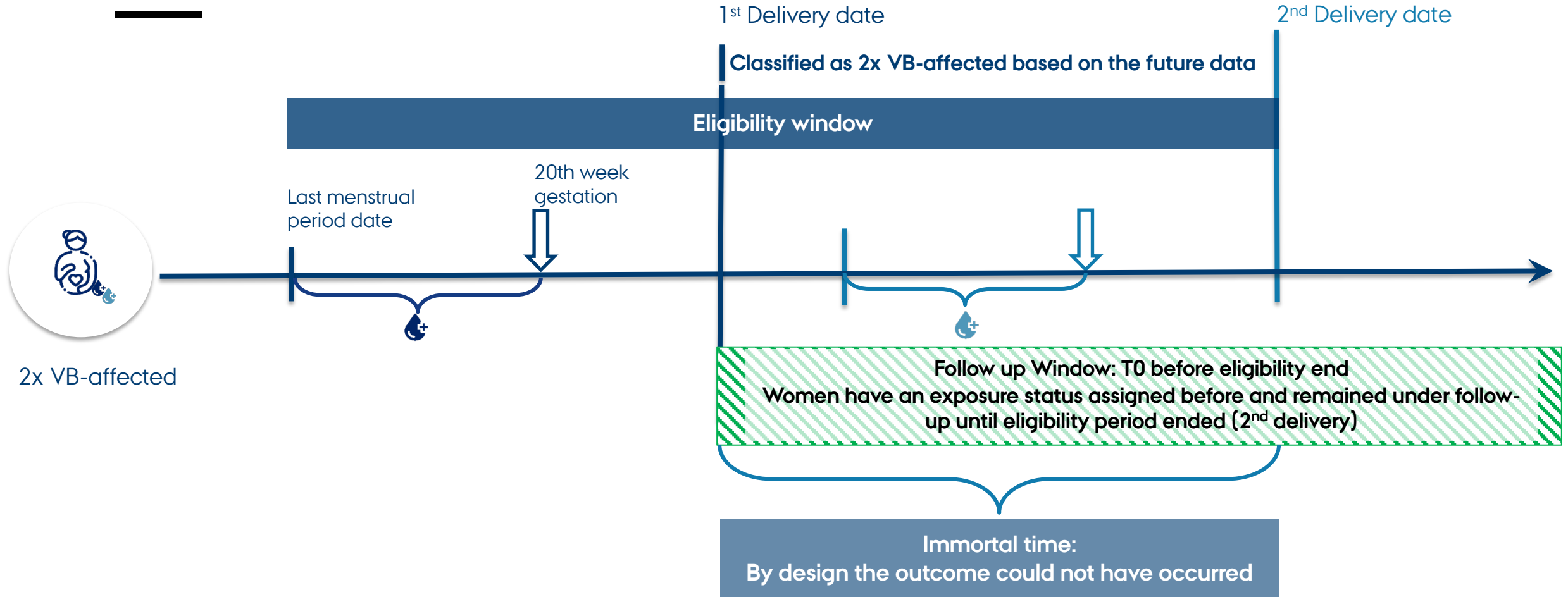


# ALL VS 1<sup>ST</sup> PREGNANCY OF A WOMAN

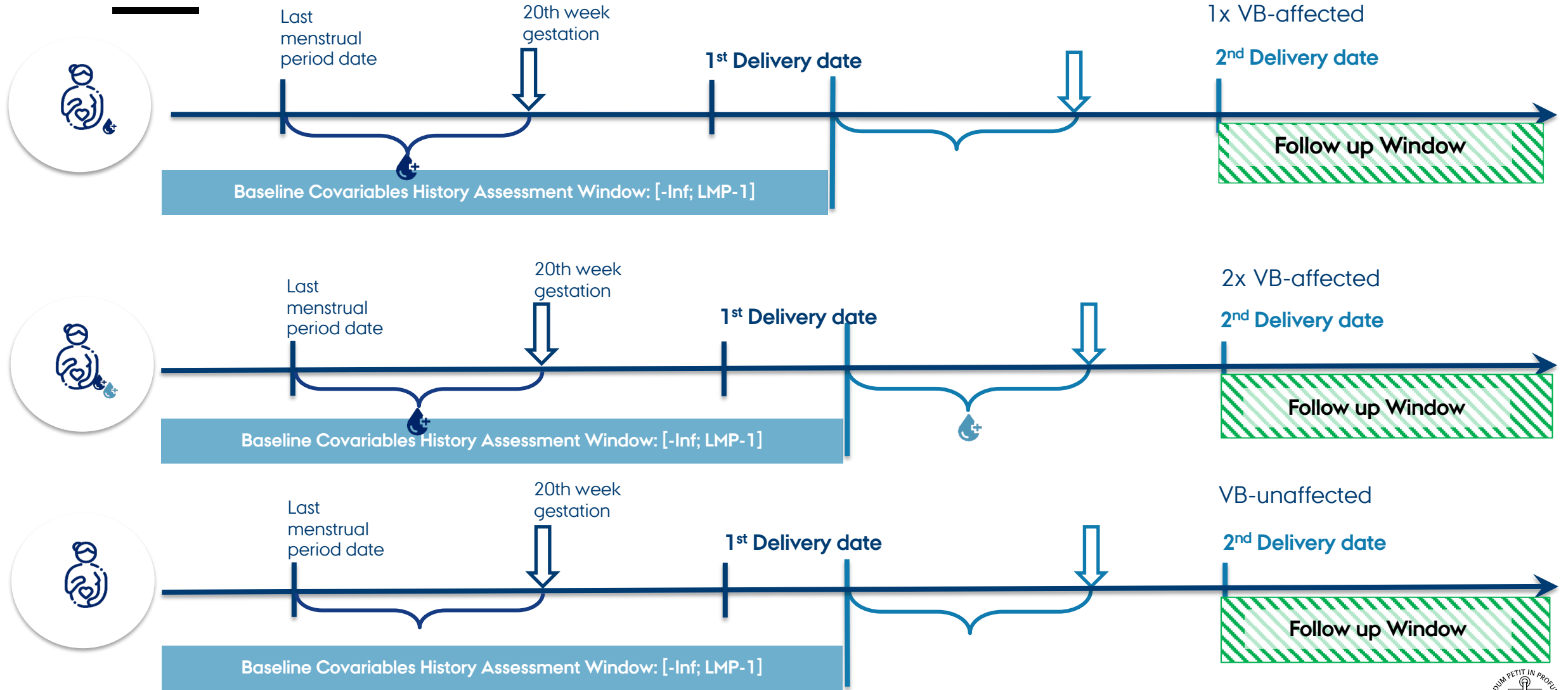




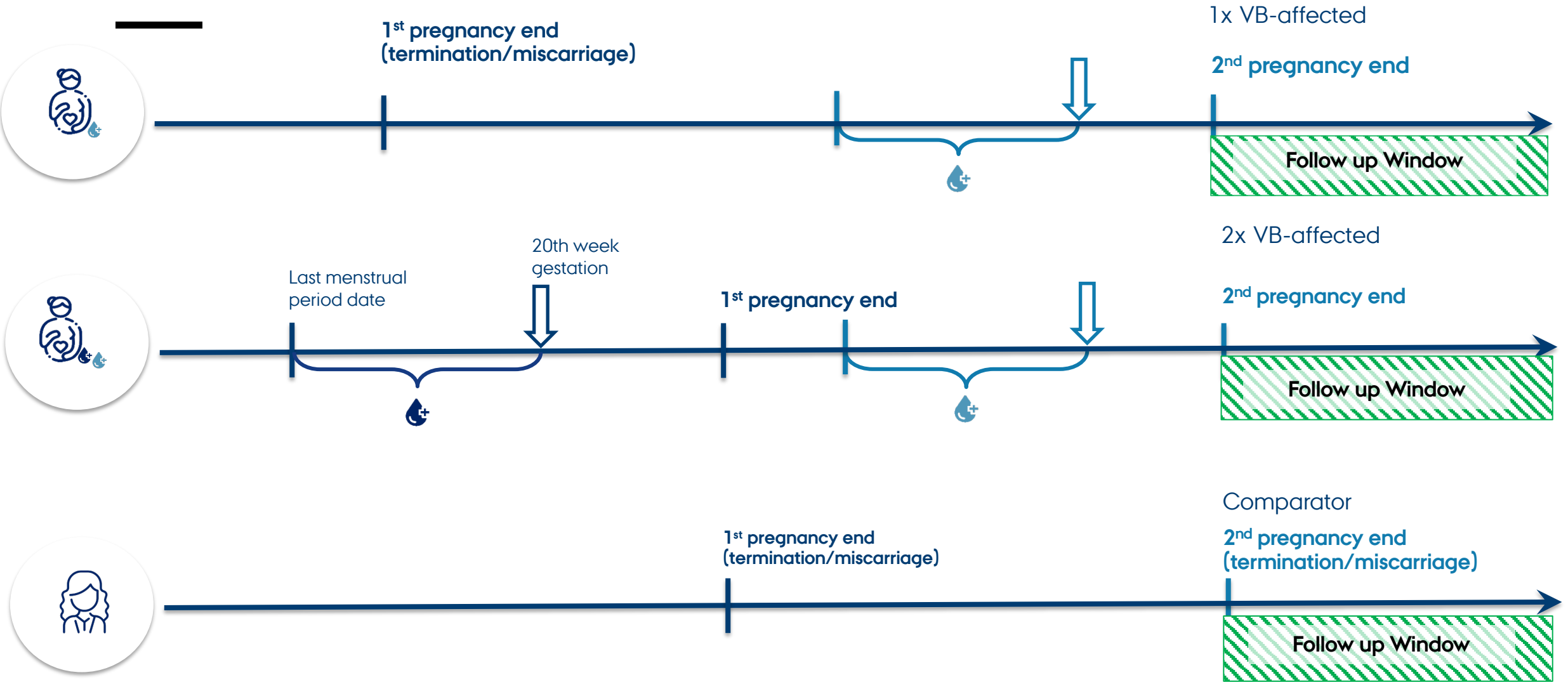
# IMMORTAL PERSON-TIME



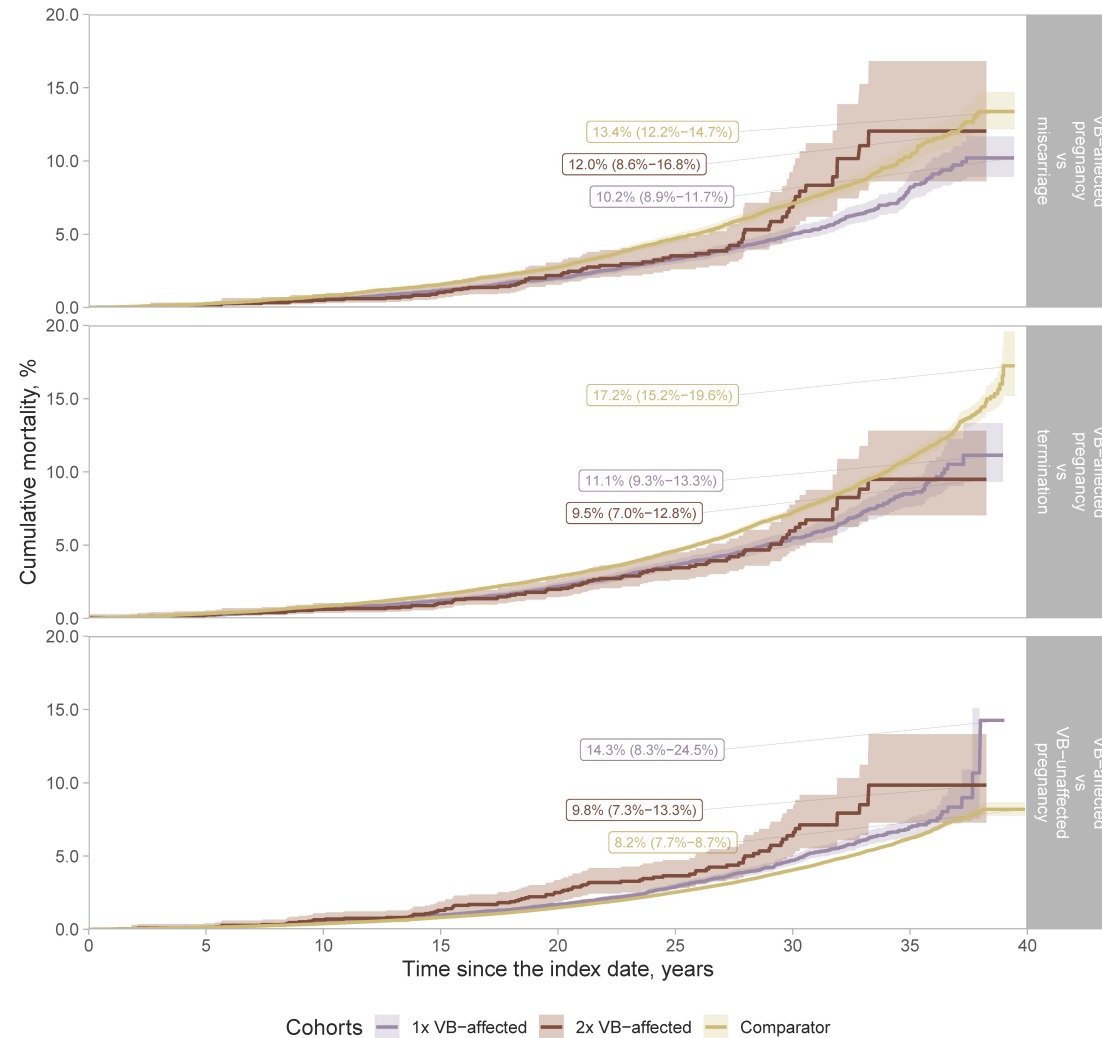
# ANALYSES OF AT LEAST 2 IDENTIFIABLE CHILDBIRTHS



# ANALYSES OF AT LEAST 2 IDENTIFIABLE CHILDBIRTHS/PREGNANCIES



# DX-RESPONSE AND ALL-CAUSE MORTALITY

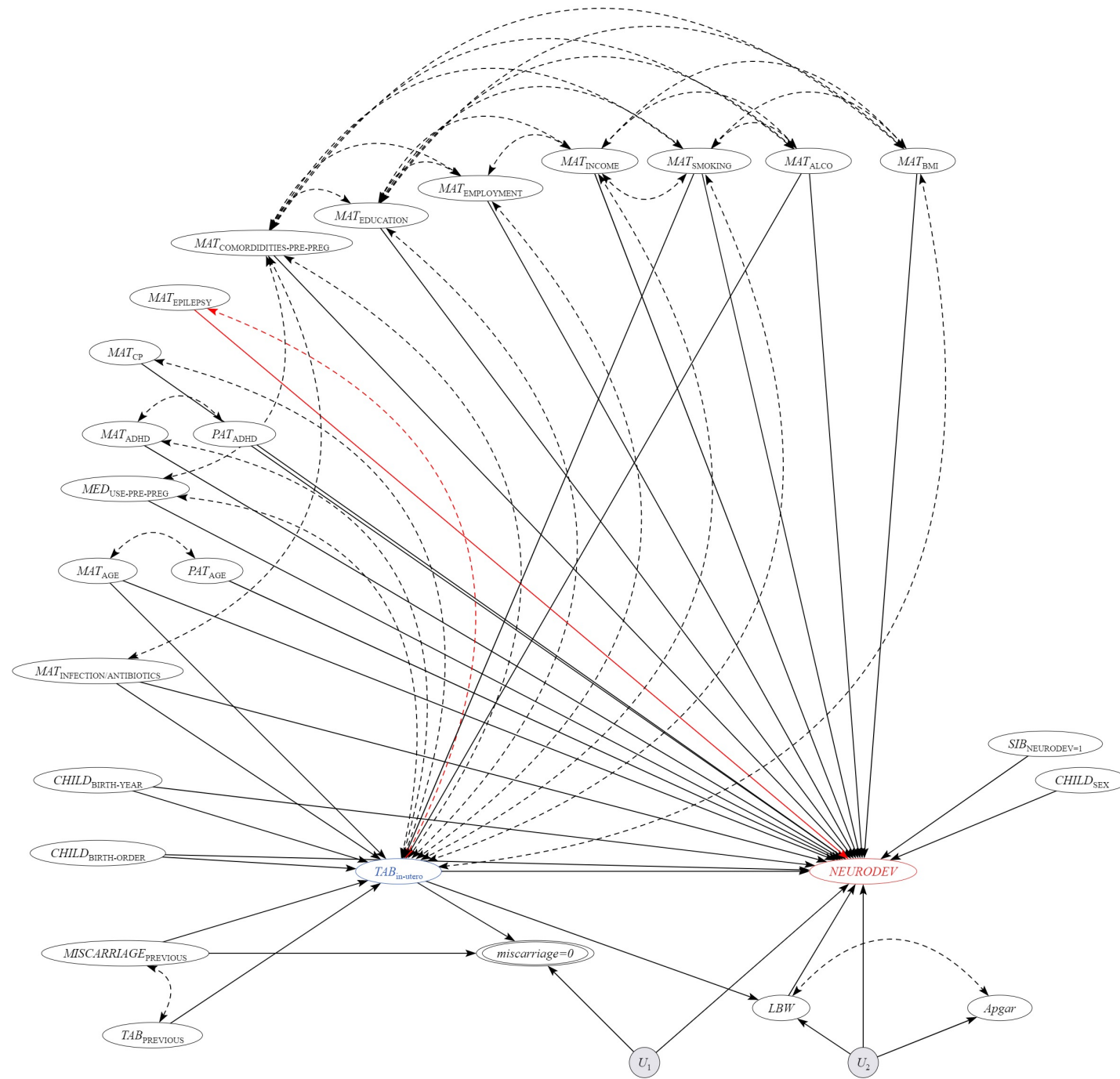


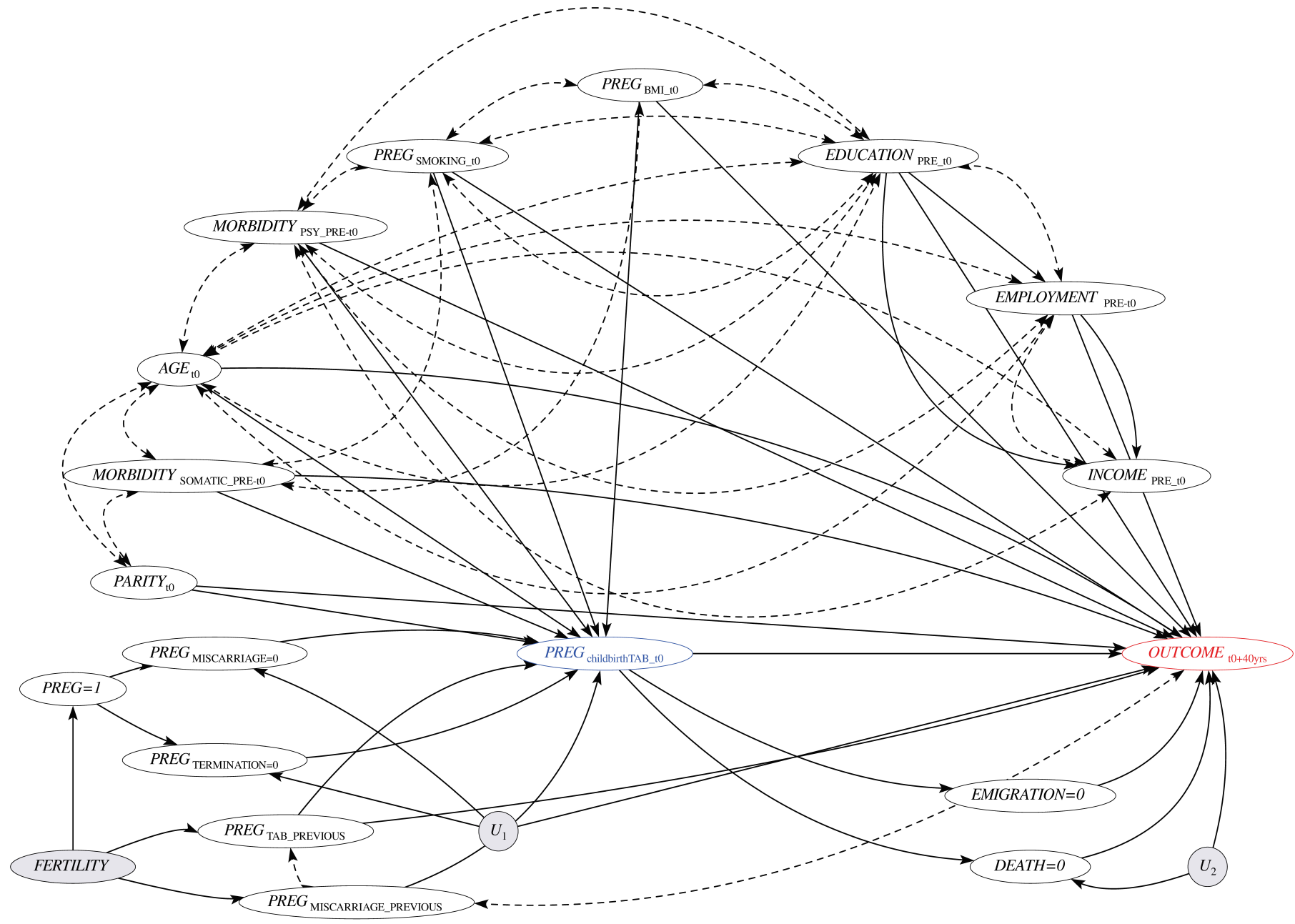
Cumulative mortality was computed using Cumulative Incidence Function (CIF) with emigration as a competing event

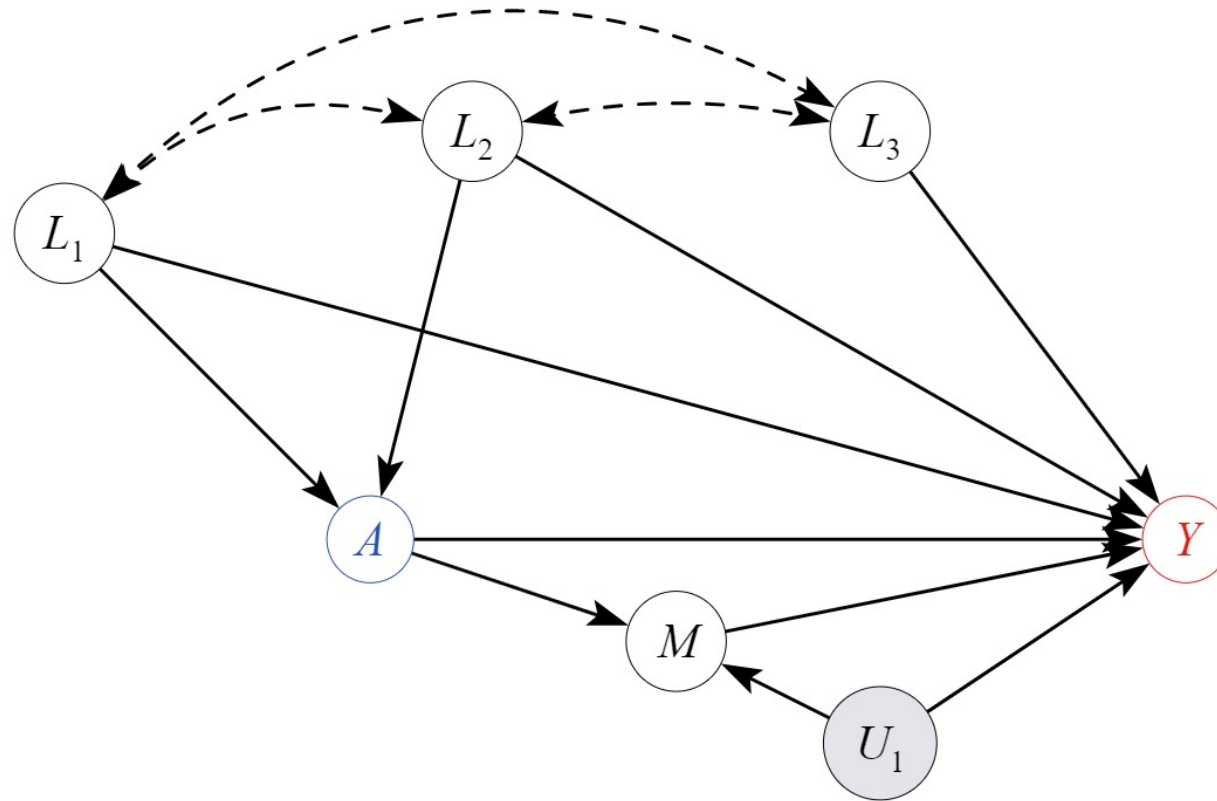




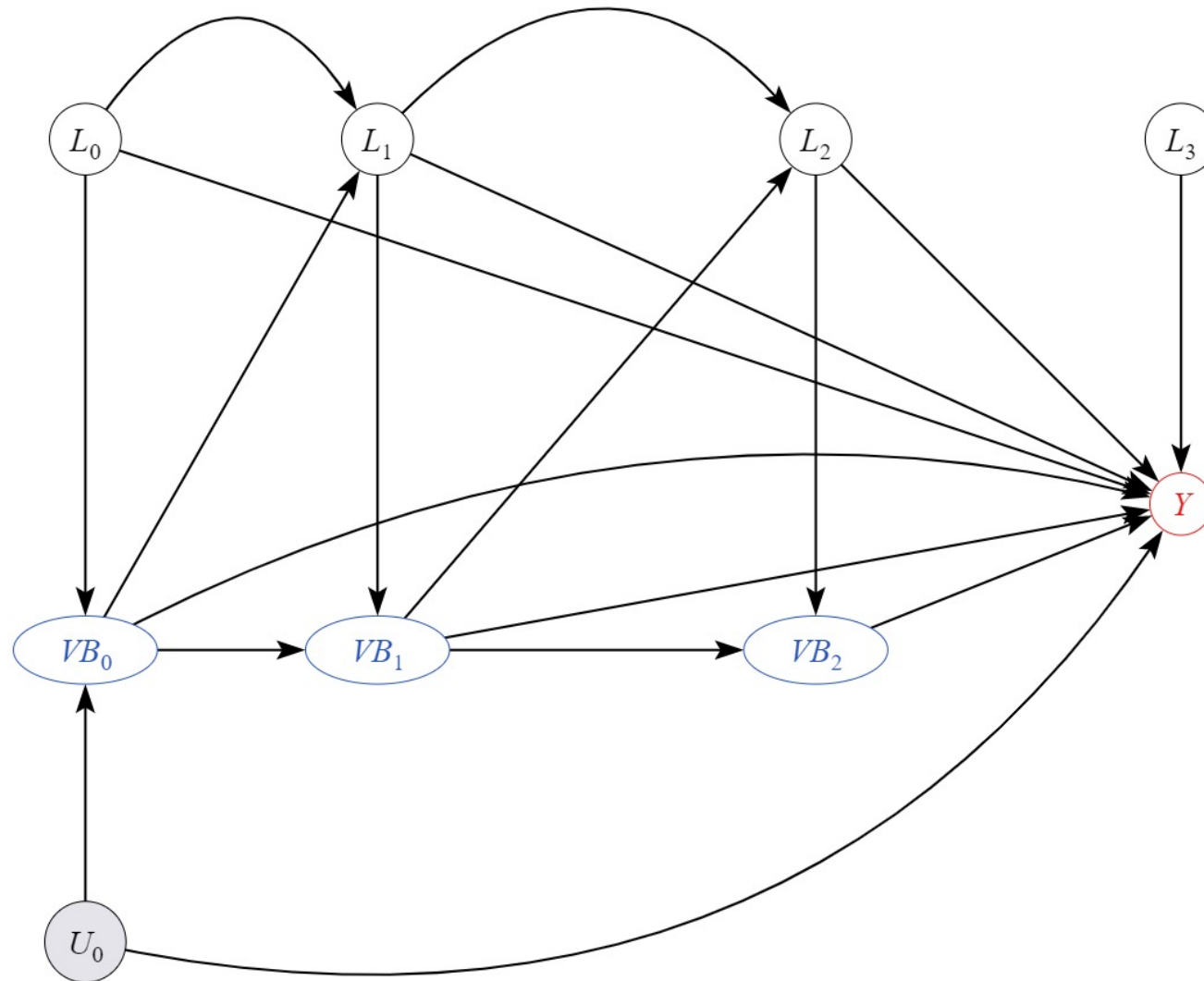
# DAGS

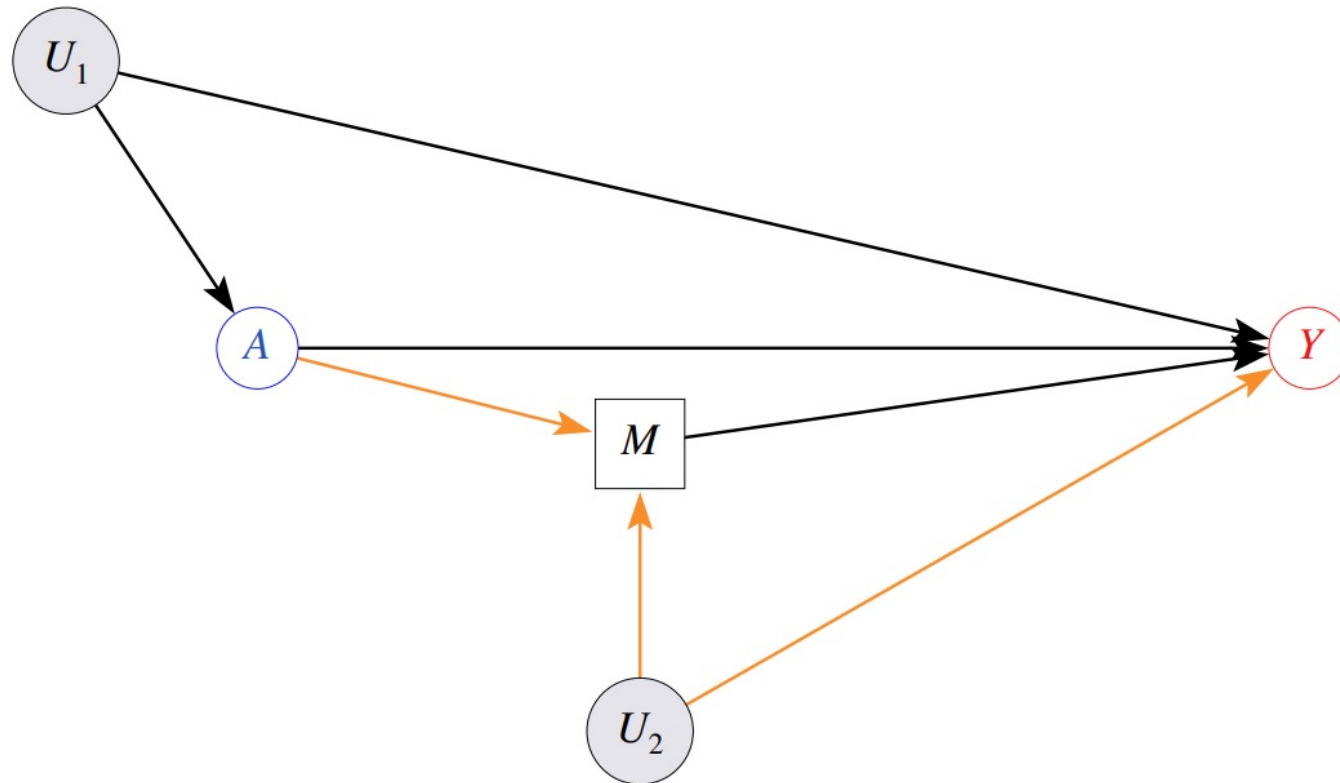












A: Pregnancy with vaginal bleeding before 12 weeks of gestation;

Y: outcomes (ischaemic heart disease, hypertension, stroke, thrombotic events, diabetes);

M: preterm delivery, prelabour rupture of membranes, foetal growth restriction, placental abruption and stillbirth;  $U_1$ : pre-pregnancy women's morbidity;

$U_2$ : a common cause of placental complications in pregnancy, preterm delivery, prelabour rupture of membranes, and cardiovascular outcomes.

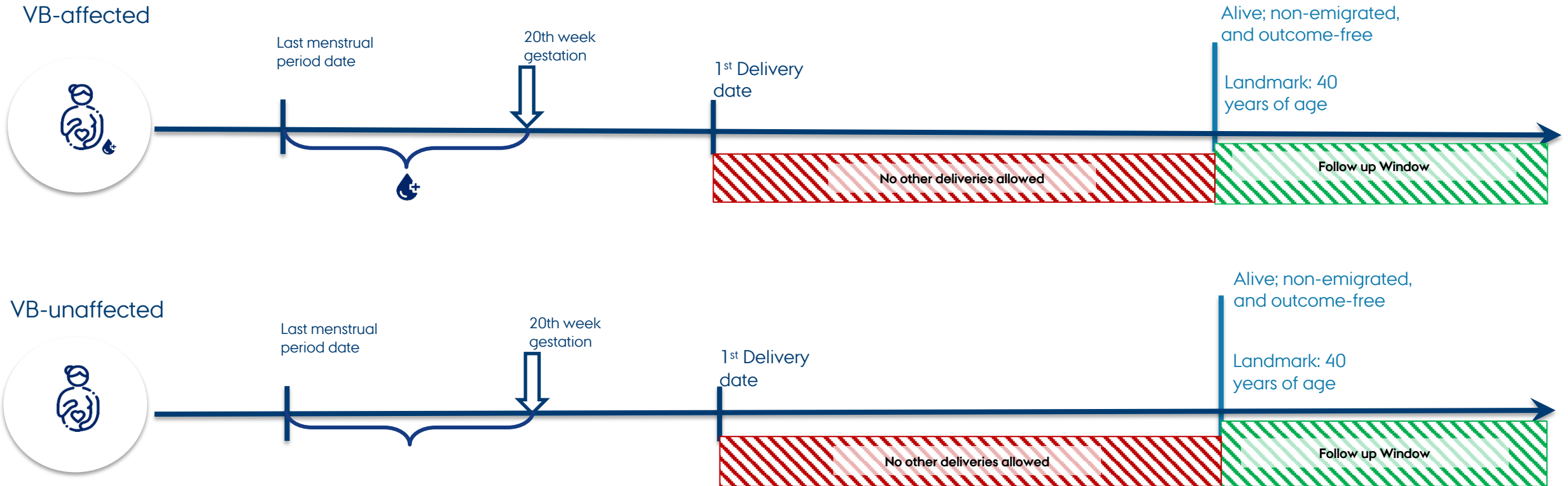
The paths 1)  $A \rightarrow [M] \leftarrow U_2 \rightarrow Y$  (in orange: collider stratification bias leading to inflation of the association between A and Y due to unmeasured  $U_2$ ) and

2)  $A \leftarrow U_1 \rightarrow Y$  (open backdoor path) are biasing the association of A on Y.



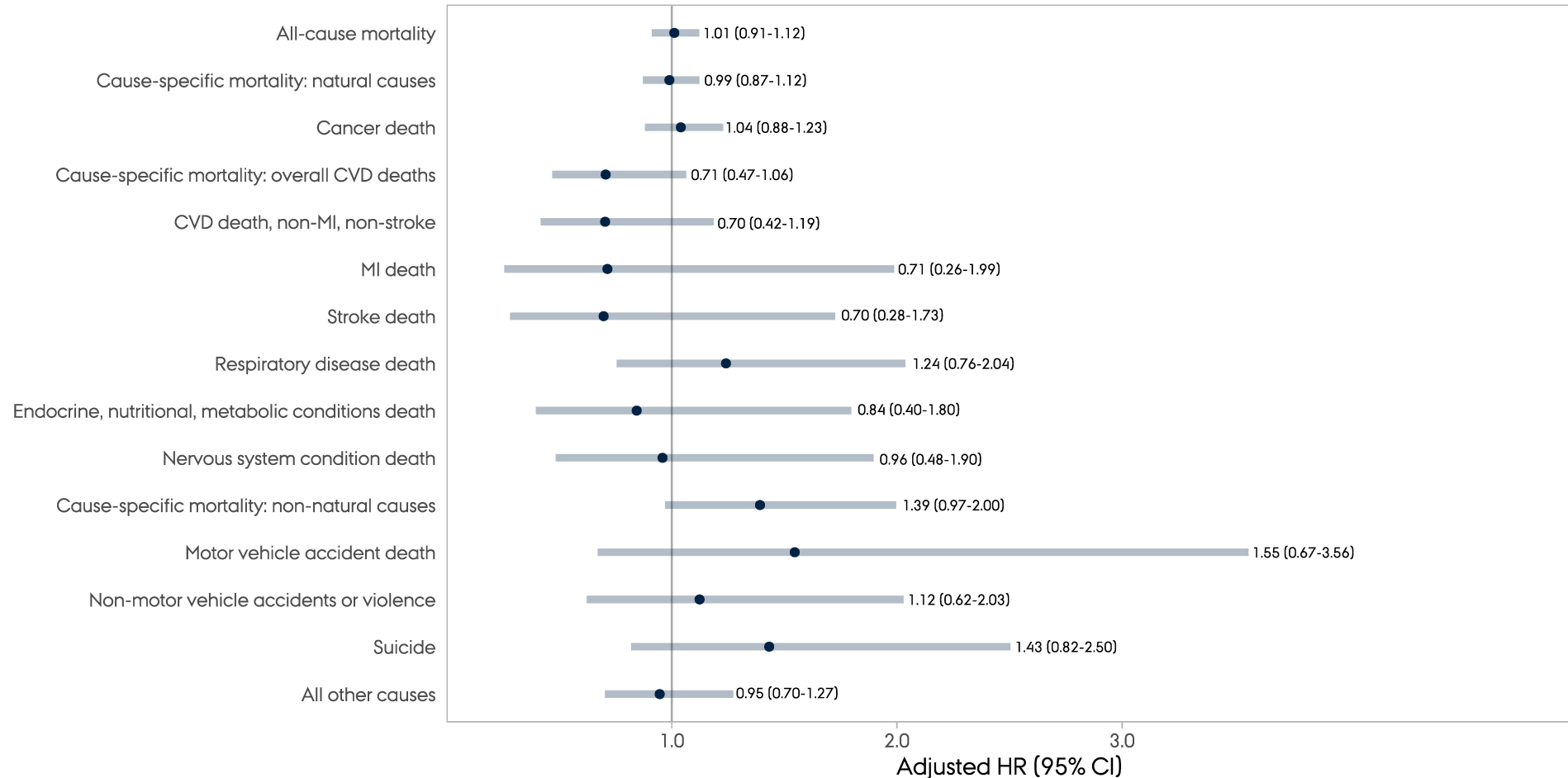
# LANDMARK ANALYSES

# ANALYSES OF 1 CHILD MOTHERS/LANDMARK ANALYSES



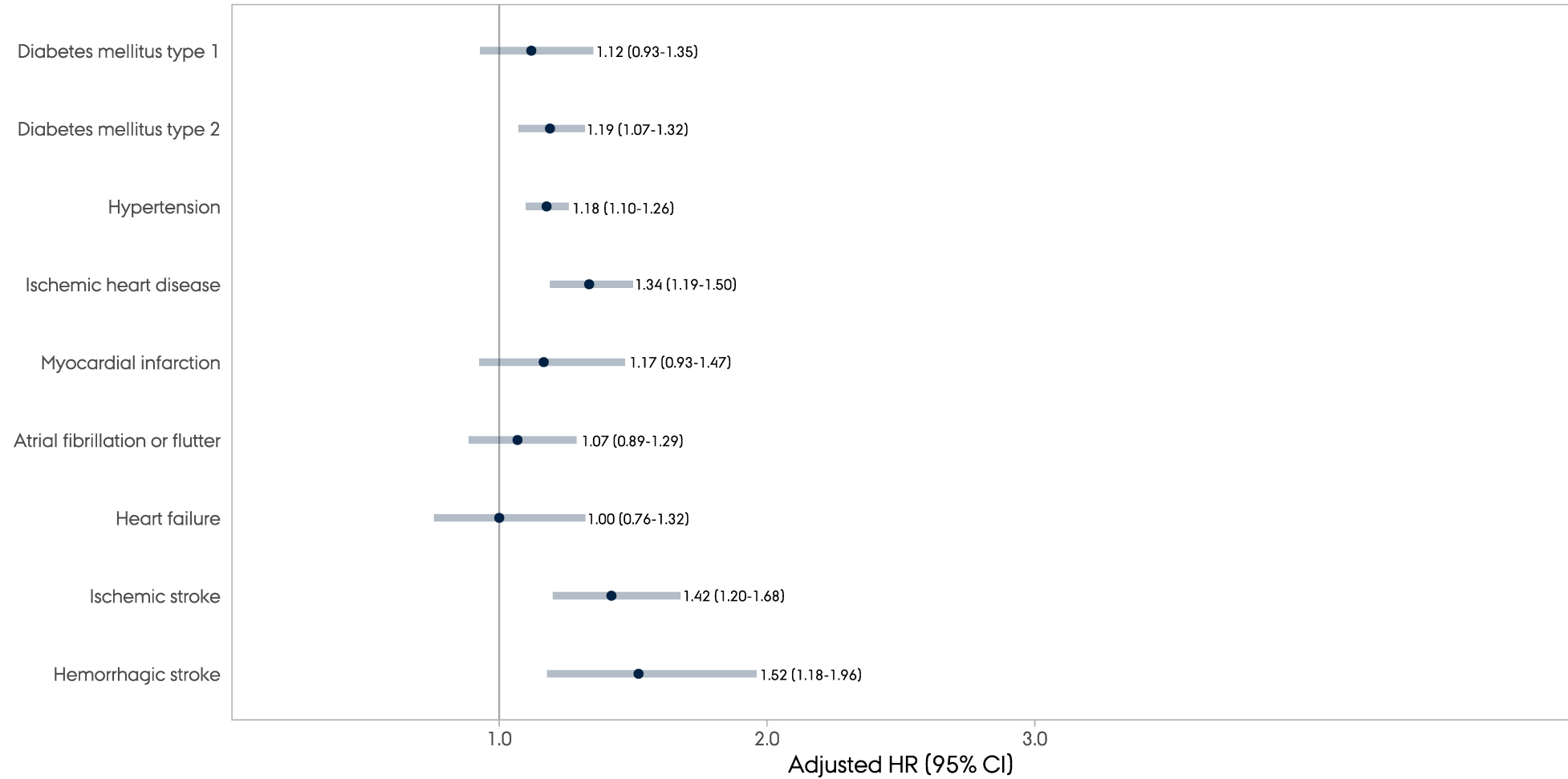
Inclusion: women with 1 delivery (VB-affected or VB-unaffected pregnancy) before the age of 40 years, outcome-free, not-emigrated and alive on the day of 40<sup>th</sup> birthday  
Exclusion: 2<sup>or</sup> more deliveries before the age of 40 years; delivery at the age of 40+

# STUDY II: LANDMARK



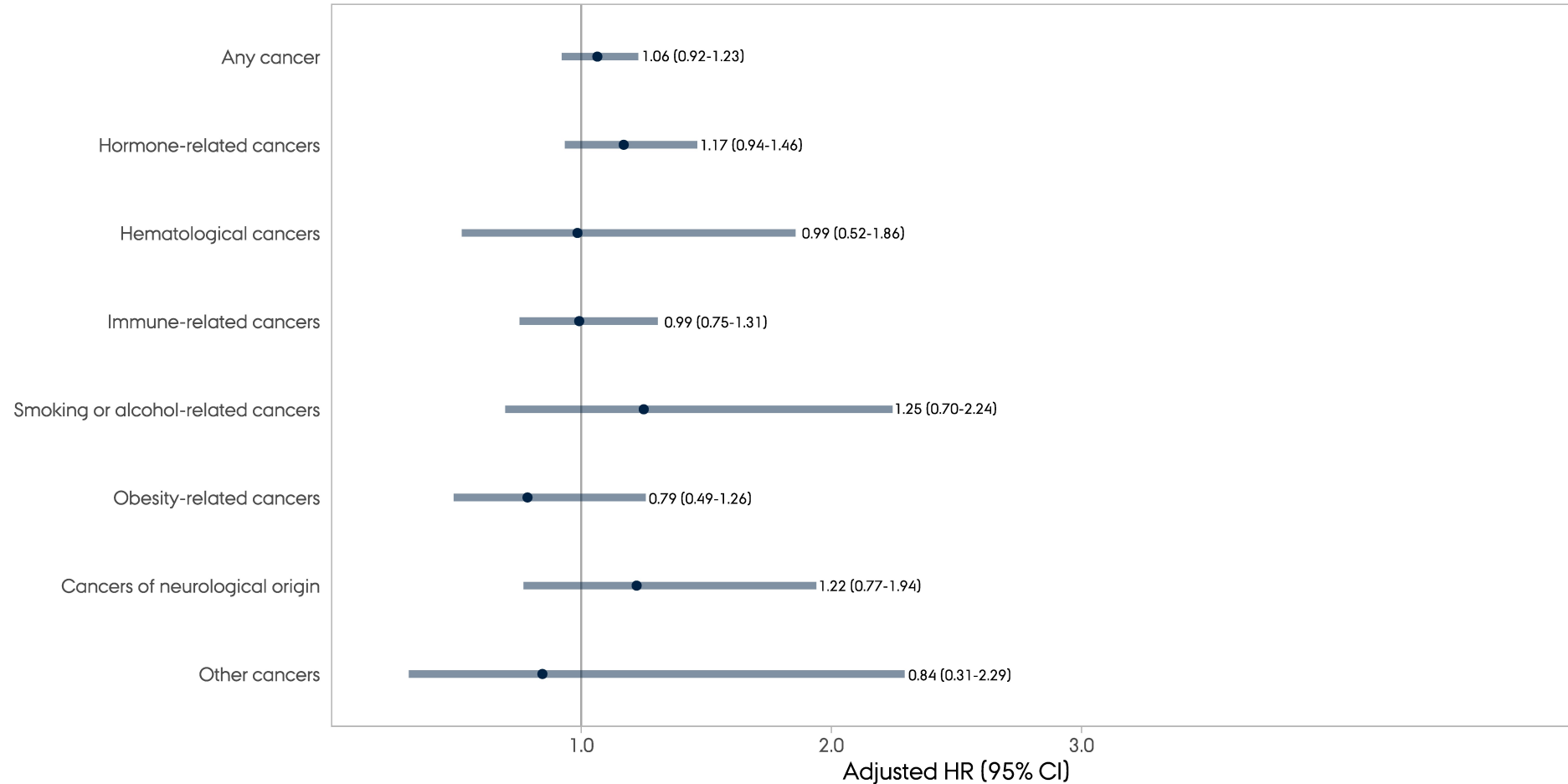
CVD, cardiovascular diseases; MI, myocardial infarction; VB, vaginal bleeding  
 By design, women having VB-exposed and VB-unexposed pregnancy and not surviving or emigrating before 35 years of age are excluded  
 Follow-up starts at 35 years of age in VB-exposed and VB-unexposed cohorts and stops at the date of emigration or death  
 Study period: 1979-2017/2018

# STUDY III: LANDMARK



CVD, cardiovascular diseases; MI, myocardial infarction; VB, vaginal bleeding  
By design, women with VB-exposed and VB-unexposed pregnancy not surviving, emigrating or experiencing CVD outcome before 40 years of age are excluded  
Follow-up starts at 40 years of age in VB-exposed and VB-unexposed cohorts and stops at the earliest of CVD outcome, emigration, or death  
Study period: 1979-2018

# STUDY IV: LANDMARK



VB, vaginal bleeding

By design, women with VB-exposed and VB-unexposed pregnancy not surviving, emigrating or experiencing cancer outcome before 40 years of age are excluded

Follow-up starts at 40 years of age in VB-exposed and VB-unexposed cohorts and stops at the earliest of cancer outcome, emigration, or death

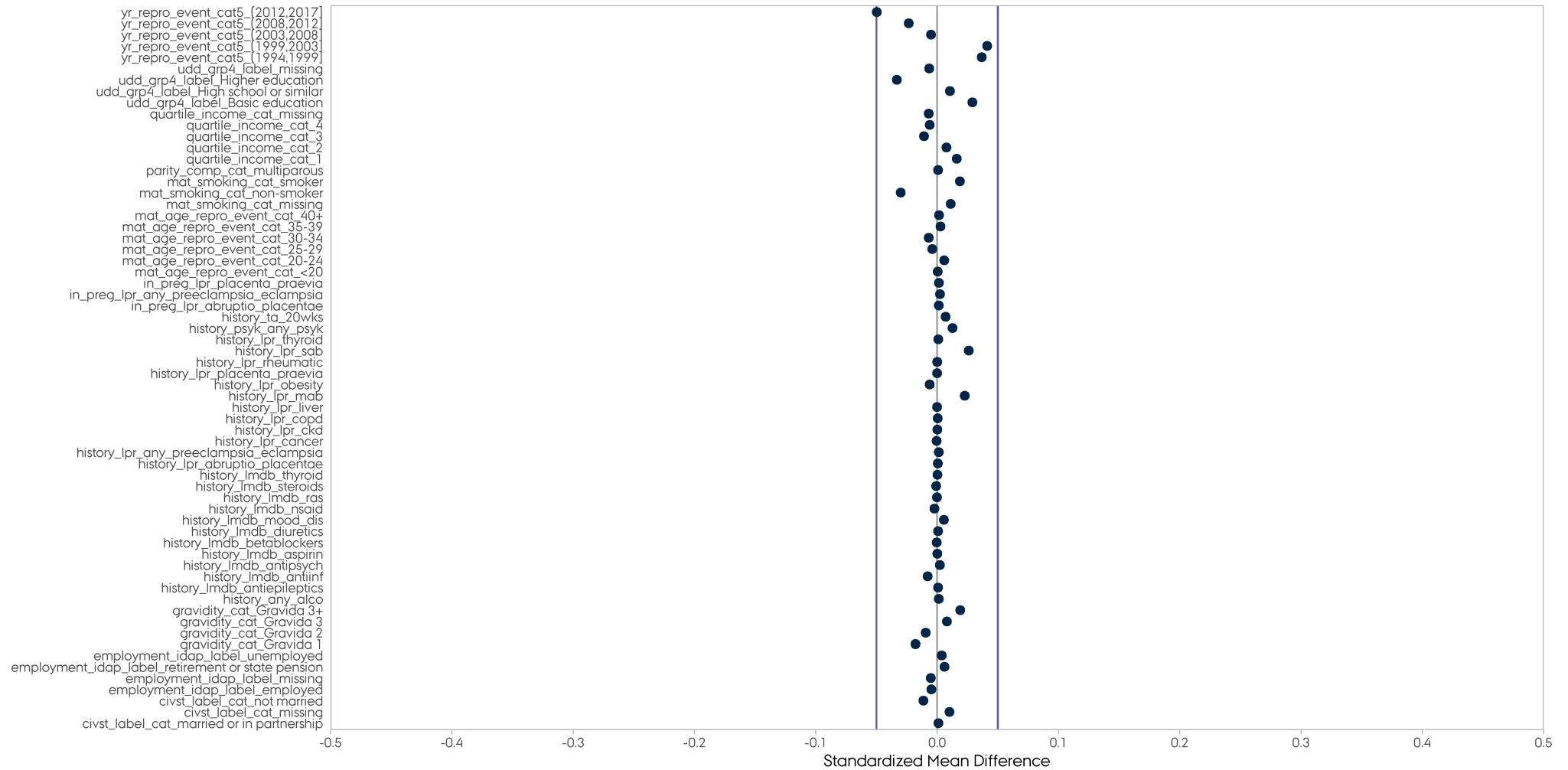
Study period: 1995-2018



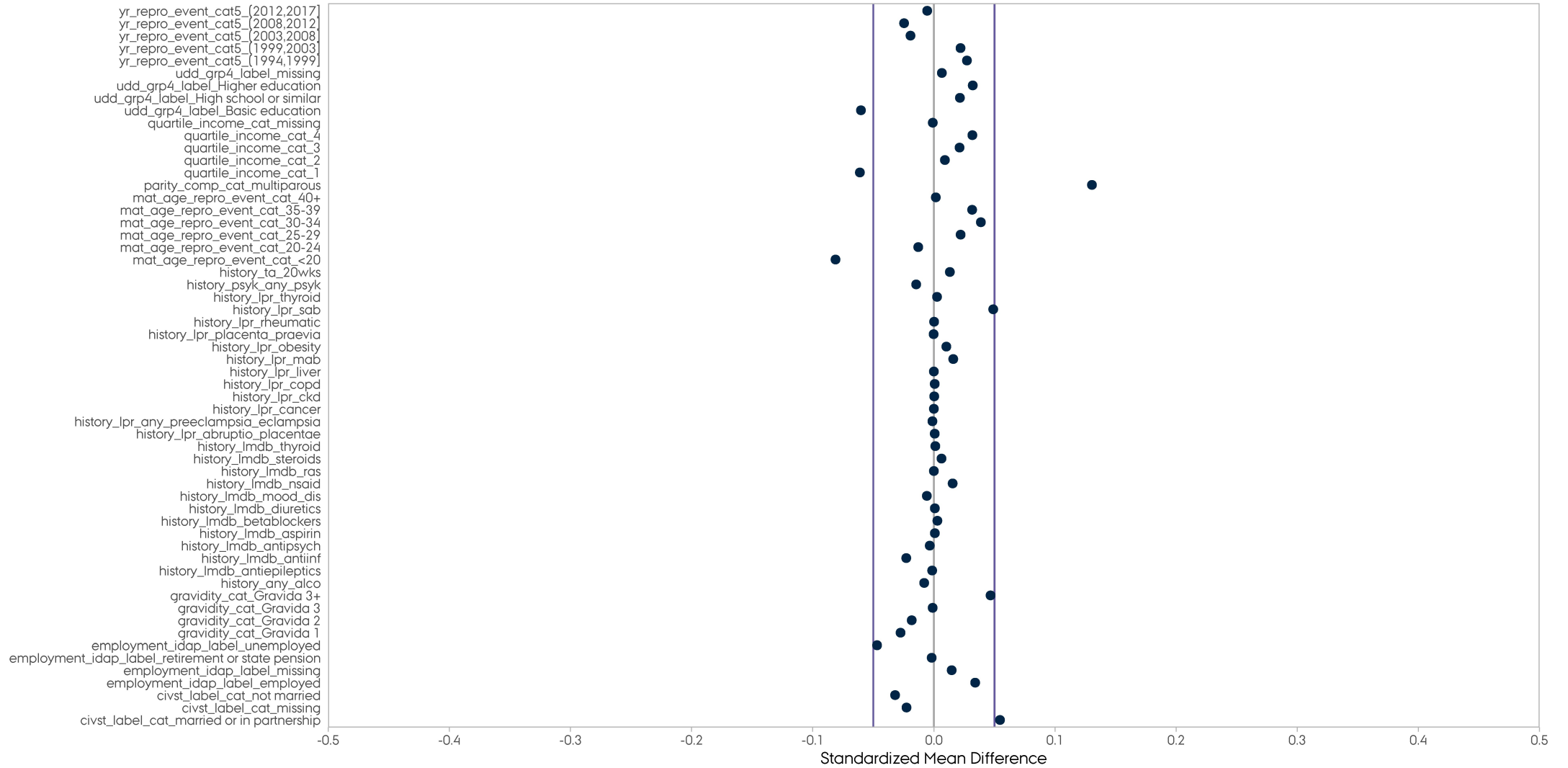
# WEIGHTING PERFORMANCE: SMD PLOTS







Study III: VB-affected vs VB-unaffected pregnancies: 1994-2018.  
 Presented SMDs are after reweighting population with IPTW (adjusted).  
 Marked cutoff point is 0.05



Study III: VB-affected pregnancies vs terminations: 1994-2018.  
 Presented SMDs are after reweighting population with IPTW (adjusted).  
 Marked cutoff point is 0.05

