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Mortality of mothers from cardiovascular and non-cardiovascular causes following pregnancy complications in first delivery

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Summary

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The combined effects of preterm delivery, small-for-gestational-age offspring, hypertensive disorders of pregnancy, placental abruption and stillbirth on early maternal death from cardiovascular causes have not previously been described in a large cohort. We investigated the effects of pregnancy complications on early maternal death in a registry-based retrospective cohort study of 782 287 women with a first singleton delivery in Denmark 1978–2007, followed for a median of 14.8 years (range 0.25–30.2) accruing 11.6 million person-years. We employed Cox proportional hazard models of early death from cardiovascular and non-cardiovascular causes following preterm delivery, small-for-gestational-age offspring and hypertensive disorders of pregnancy.

We found that preterm delivery and small-for-gestational-age were both associated with subsequent death of mothers from cardiovascular and non-cardiovascular causes. Severe pre-eclampsia was associated with death from cardiovascular causes only. There was a less than additive effect on cardiovascular mortality hazard ratios with increasing number of pregnancy complications: preterm delivery 1.90 [95% confidence intervals 1.49, 2.43]; preterm delivery and small-for-gestational-age offspring 3.30 [2.25, 4.84]; preterm delivery, small-for-gestational-age offspring and pre-eclampsia 3.85 [2.07, 7.19]. Thus, we conclude that, separately and combined, preterm delivery and small-for-gestational-age are strong markers of early maternal death from both cardiovascular and non-cardiovascular causes, while hypertensive disorders of pregnancy are markers of early death of mothers from cardiovascular causes.

Keywords: *fetal growth restriction*, *hypertensive disorders of pregnancy*, *placental abruption*, *preterm delivery*, *stillbirth*, *mortality of mothers*.

Introduction

Pregnancy outcomes such as preterm delivery, small-for-gestational-age (SGA) offspring, pre-eclampsia, placental abruption or stillbirth occur in approximately 8% of all deliveries in Denmark. These complications often occur concurrently: preterm delivery is frequently indicated in pregnancies complicated by severe pre-eclampsia or SGA.[1] SGA is commonly observed in pre-eclamptic pregnancies,[2] and pre-eclampsia is a risk factor for stillbirth and placental abruption.[3,4]

The clustering and shared predisposing factors of these conditions have led to the conception of a 'placenta associated syndrome'. This syndrome can produce both maternal or fetal symptoms, i.e. either pre-eclampsia or fetal growth restriction.[5] Although preterm delivery, placental abruption and stillbirth can be regarded as severity indicators of the syndrome, they may also represent different disease entities.

While the precise aetiology of these pregnancy complications remains elusive, a growing understanding

of their pathogenic mechanisms has emerged.[3–8] Recently, circulating levels of anti-angiogenic factors have been shown to be elevated early in normal pregnancies compared with pregnancies complicated by a placental syndrome;[9] in contrast, levels of these anti-angiogenic factors increase more rapidly later in pregnancies subsequently complicated by pre-eclampsia.[10] The finding that such increased levels may precede the other pregnancy complications, together with the shared histopathological findings frequently identified among cases of related adverse pregnancy outcomes suggest a shared pathogenetic mechanism.[11–13]

These pregnancy complications have also been linked to the metabolic syndrome, a major risk factor for cardiovascular disease.[14,15] Also, several studies have linked pregnancy complications to later cardiovascular events in the mother.[16–18] Few of these studies, however, have utilised a large longitudinal cohort design or investigated several pregnancy complications in one cohort, or the risk of non-cardiovascular in contrast to cardiovascular causes of death. We have therefore designed a registry-based retrospective cohort study to elucidate the impact of preterm delivery, delivery of an SGA offspring, hypertensive disorders of pregnancy, placental abruption and stillbirth in a first delivery on subsequent rates of death from cardiovascular and non-cardiovascular and all causes.

Materials and methods

The National Patient Registry (NPR) collects information on all discharge diagnoses from hospitals and deliveries in Denmark. Since 1978, the registry has had complete national coverage and since 1994, it has included diagnoses from outpatient clinics as well.[19] Discharging physicians code each medical diagnosis (one or more per visit) using the International Classification of Diseases (ICD). We linked information in the NPR with the Danish Central Person Registry and Cause of Death Registry retrieving status on emigration and death at 1 March 2008.

Information on all singleton deliveries in Denmark from 1 January 1978 to 1 October 2007 was extracted yielding 1 795 806 deliveries to 965 475 women. Of these, we included women aged 15–50 years with a first delivery only ($n = 796\,915$), and excluded women with any preceding cardiovascular diagnosis (e.g. hypertension or deep venous thromboembolism; see supporting information) ($n = 11\,605$; 1.5%), diabetes mellitus types 1 and 2 ($n = 2387$; 0.3%) and women deceased or emigrated within 3 months of delivery ($n = 65$ and $n = 571$). Thus, the study cohort consisted of 782 287 women.

The exposures were preterm delivery, SGA offspring, hypertensive disorders of pregnancy, placental abruption and stillbirth. The hypertensive disorders of pregnancy, placental abruption, stillbirth, causes of death and cardiovascular diseases were ascertained by the specific ICD-8 and -10 codes for these diagnoses (see supporting information). Preterm delivery was defined as a delivery before 37 completed weeks of gestation. In earlier years, the gestational age was estimated from the last menstrual period; gradually, in later years, the gestation was estimated using early second trimester sonography. Fetal growth was estimated using birthweight standardised for gender and gestational age;[20] SGA and large-for-gestational-age were defined as fetal growth 2 SD below or above the mean, respectively. Implausible values of birthweight, gestational age, fetal growth and the combination of these were reassigned as missing values. Missing values occurred more frequently in the earlier years; these were analysed as separate groups.

The hypertensive disorders of pregnancy were stratified into gestational hypertension, mild pre-eclampsia and severe pre-eclampsia (including eclampsia and the HELLP syndrome); the definition of these have changed little during the 30 study years,[21] and the overall frequency in the NPR has remained stable. The accuracy of the hypertensive diagnoses in the NPR has been validated several times revealing specificities over 99% for all types, but sensitivities of 10% for gestational hypertension, 44% for severe pre-eclampsia, and 69% for mild and severe pre-eclampsia combined;[21] positive predictive values (PPV) comprised 56% for gestational hypertension, 100% for severe pre-eclampsia, and 74% for mild and severe pre-eclampsia combined. When pre-eclampsia occurred with a preterm delivery, the sensitivity of the pre-eclampsia designation was 75%.[22]

When investigating combinations of preterm delivery, SGA and pre-eclampsia, we dichotomised hypertensive disorders of pregnancy into two groups: pre-eclampsia and no-pre-eclampsia (the latter being the reference group, which included gestational hypertension). We did so because of the low sensitivity of gestational hypertension, the large size of the normotensive group and the need to differentiate pre-eclampsia from gestational hypertension.

The end points were death from all causes, which was also subdivided into death from cardiovascular causes and non-cardiovascular causes. We restrictively defined a cardiovascular cause of death as either stated thus in the Cause of Death Registry, or a first cardiovascular diagnosis, e.g. *de novo* hypertension or ischaemic heart disease, reported within 1 week prior to the time of death. We defined a non-cardiovascular cause of death as a death without any previous cardiovascular diagnosis, e.g. women dying of trauma or cancer. The intermediate group of deceased women with a previous cardiovascular diagnosis, but no new diagnoses 7 days prior to the time of death, e.g. women previously diagnosed with hypertension who died of cancer, was not analysed separately, but was included in the end point of death from all causes. We censored women who had emigrated at the time of departure.

The Cox proportional hazard models were employed with time from delivery to event or censoring (i.e. death or emigration) as the time-dependent variable, and controlled for maternal age at delivery and year of delivery in all the models. After initial stratification in the models, we included interaction terms in a forward stepwise procedure using likelihood ratio statistics with an entry criterion of $P < 0.05$.

We present the unadjusted number, percentage and rate per 10 000 years of observation; all hazard ratios (HR) are presented with 95% confidence intervals (CI). SPSS (v16.0 for Macintosh, SPSS Inc.; Chicago, IL, USA) was used for all calculations. The study was approved by the Danish Data Protection Agency.

Table 1. Baseline characteristics

Maternal age at delivery, years (mean, SD)	26.8	(SD 4.6)
Birthweight, g (mean, SD)	3394	(SD 566)
Gestational age, days (mean, SD)	279.8	(SD 13.6)
37 weeks and above	713 739	91.2%
32–36 weeks	35 255	4.5%
28–31 weeks	4698	0.6%
20–27 weeks	1706	0.2%
Missing values	26 889	3.4%
Small-for-gestational-age (SGA)	43 109	5.5%
Appropriate-for-gestational-age (AGA)	691 267	88.4%
Large-for-gestational-age (LGA)	11 646	1.5%
Missing values	36 265	4.6%
Hypertensive disorders of pregnancy	41 275	5.3%
Gestational hypertension	7449	1.0%
Pre-eclampsia	33 826	4.3%
Mild pre-eclampsia	26 810	3.4%
Severe pre-eclampsia	7016	0.9%
Placental abruption	7684	1.0%
Stillbirth	4039	0.5%
Censoring		
Emigrated	15 902	2.0%
Deceased	8 876	1.1%
Deceased from cardiovascular causes	1 310	0.2%
Deceased from non-cardiovascular causes	5 776	0.7%
Follow-up time, years (median, range)	14.63	(0.25–30.2)
Person-years	11 600 945	
Maternal age at censoring, years (mean, SD)	41.6	(SD 8.3)

Unless stated otherwise, the numbers refer to the number of women (*n*) and the percentage of the total population.

Results

Baseline characteristics are shown in Table 1. The number of women having one or more of the outcomes of preterm delivery, SGA and hypertensive disorder was 108 230 (14.5%). Out of women who had gestational hypertension, mild pre-eclampsia and severe pre-eclampsia, 13%, 14% and 53%, respectively, also delivered preterm and/or had an SGA offspring.

Table 2 shows the mortality of women experiencing pregnancy complications. In general, preterm delivery, SGA offspring and hypertensive disorders of pregnancy were more strongly associated with death from cardiovascular causes than non-cardiovascular causes. The hypertensive disorders also showed a non-significant decrease in risk of death from non-cardiovascular causes. The HRs of placental abruption and stillbirth were equal for death from cardiovascular and non-cardiovascular causes, albeit the HR for death from cardiovascular causes was non-significant.

Table 3 shows the combinations of preterm delivery, SGA and pre-eclampsia (mild and severe pre-eclampsia combined) and subsequent mortality. This illustrates the additive effects of having more than one pregnancy complication, and the differences between the causes of death: women having preterm delivery and SGA had an increased risk of death from all causes compared with women having either of these two complications. Women having pre-eclampsia did not have increased overall mortality, although in combination with preterm delivery and SGA, the mortality increased but still not more than in non-pre-eclamptic women.

Table 2. Women experiencing pregnancy complications and the risk of subsequent death

	All women		Death from all causes					
Pregnancy outcomes	*n*	%	*n*	%	rate	HR	CI	*P*
Preterm delivery	41 659	5.3%	675	1.6%	11.7	1.66	[1.53, 1.79]	<0.001
Small-for-gestational-age	43 109	5.5%	1002	2.3%	14.2	1.91	[1.79, 2.04]	<0.001
Gestational hypertension	7449	1.0%	115	1.5%	10.3	1.23	[1.03, 1.48]	0.001
Mild pre-eclampsia	26 810	3.4%	364	1.4%	8.7	1.11	[1.00, 1.23]	
Severe pre-eclampsia	7016	0.9%	84	1.2%	9.2	1.38	[1.11, 1.71]	
Placental abruption	7684	1.0%	147	1.9%	11.4	1.41	[1.20, 1.67]	<0.001
Stillbirth	4039	0.5%	98	2.4%	15.6	1.83	[1.50, 2.23]	<0.001
	All women		Death from cardiovascular causes					
Pregnancy outcomes	*n*	%	*n*	%	rate	HR	CI	*P*
Preterm delivery	41 659	5.3%	115	0.3%	2.0	1.98	[1.64, 2.40]	<0.001
Small-for-gestational-age	43 109	5.5%	190	0.4%	2.7	2.56	[2.19, 3.00]	<0.001
Gestational hypertension	7449	1.0%	32	0.4%	2.9	2.47	[1.74, 3.52]	<0.001
Mild pre-eclampsia	26 810	3.4%	92	0.3%	2.2	1.99	[1.61, 2.47]	
Severe pre-eclampsia	7016	0.9%	24	0.3%	2.6	2.89	[1.93, 4.33]	
Placental abruption	7684	1.0%	19	0.2%	1.5	1.23	[0.78, 1.93]	0.37
Stillbirth	4039	0.5%	14	0.3%	2.2	1.80	[1.06, 3.01]	0.029
	All women		Death from non-cardiovascular causes					
Pregnancy outcomes	*n*	%	*n*	%	rate	HR	CI	*P*
Preterm delivery	41 659	5.3%	398	1.0%	6.9	1.48	[1.34, 1.64]	<0.001
Small-for-gestational-age	43 109	5.5%	578	1.3%	8.2	1.66	[1.53, 1.82]	<0.001
Gestational hypertension	7449	1.0%	50	0.7%	4.5	0.82	[0.62, 1.08]	0.11
Mild pre-eclampsia	26 810	3.4%	187	0.7%	4.4	0.86	[0.74, 1.00]	
Severe pre-eclampsia	7016	0.9%	41	0.6%	4.5	1.00	[0.74, 1.36]	
Placental abruption	7684	1.0%	105	1.4%	8.1	1.56	[1.29, 1.89]	<0.001
Stillbirth	4039	0.5%	62	1.5%	9.9	1.79	[1.39, 2.30]	<0.001

Maternal age and year of delivery were included in all models.
Rate is number of events per 10 000 years of observation.
CI, 95% confidence interval; HR, hazard ratio.

The cardiovascular mortality was increased in women delivering preterm (HR 1.90), having an SGA offspring (HR 2.51) or having pre-eclampsia only (HR 2.08); there was an additive effect on cardiovascular mortality, when experiencing combinations of these.

The non-cardiovascular mortality was also increased following preterm delivery (HR 1.44), SGA (HR 1.66) and the combination of these (HR 2.12). In pre-eclamptic women, there was a small non-significant reduced mortality (HR 0.89); adding preterm delivery, this effect was diminished (HR 1.05), and when adding SGA the mortality increased non-significantly (HR 1.36); having all three conditions increased the mortality to HR 1.48.

In the stratified analysis, placental abruption had no effect on the risk of death from all causes in non-pre-eclamptic women (HR 1.06 [0.88, 1.26]); in pre-eclamptic women, it increased the mortality by a HR 2.08 [1.27, 3.40]. Stillbirth had no effect on the overall mortality in pre-eclamptic women (HR 1.03 [0.42, 2.51]); in non-pre-eclamptic women, stillbirth increased the mortality by HR 1.28 [1.04, 1.58]. In all other stratifications, the number of events was reduced thereby limiting the statistical power (data not shown).

Table 3. Combinations of preterm delivery, small-for-gestational age, and pre-eclampsia and the risk of subsequent death

	All women		Death from all causes					
Pregnancy outcomes	*n*	%	*n*	%	rate	HR	CI	*P*
None	643 935	82.3%	6201	1.0%	6.7	1.00	[reference]	<0.001
PTD	31 132	4.0%	441	1.4%	10.4	1.58	[1.44, 1.74]	
SGA	33 311	4.3%	755	2.3%	13.7	1.88	[1.74, 2.03]	
PTD + SGA	5206	0.7%	150	2.9%	18.0	2.45	[2.08, 2.88]	
Pre-eclampsia	25 184	3.2%	285	1.1%	7.5	1.10	[0.97, 1.24]	
Pre-eclampsia + PTD	2662	0.3%	31	1.2%	9.4	1.60	[1.13, 2.28]	
Pre-eclampsia + SGA	2374	0.3%	55	2.3%	14.4	2.02	[1.55, 2.63]	
Pre-eclampsia + PTD + SGA	2218	0.3%	42	1.9%	13.7	2.11	[1.56, 2.86]	
Missing values	36 265	4.6%	916	2.5%	11.0	1.08	[1.00, 1.16]	
	All women		Death from cardiovascular causes					
Pregnancy outcomes	*n*	%	*n*	%	rate	HR	CI	*P*
None	643 935	82.3%	824	0.1%	0.9	1.00	[reference]	<0.001
PTD	31 132	4.0%	70	0.2%	1.7	1.90	[1.49, 2.43]	
SGA	33 311	4.3%	136	0.4%	2.5	2.51	[2.10, 3.01]	
PTD + SGA	5206	0.7%	27	0.5%	3.2	3.30	[2.25, 4.84]	
Pre-eclampsia	25 184	3.2%	72	0.3%	1.9	2.08	[1.63, 2.64]	
Pre-eclampsia + PTD	2662	0.3%	6	0.2%	1.8	2.41	[1.08, 5.37]	
Pre-eclampsia + SGA	2374	0.3%	17	0.7%	4.5	4.67	[2.89, 7.55]	
Pre-eclampsia + PTD + SGA	2218	0.3%	10	0.5%	3.3	3.85	[2.07, 7.19]	
Missing values	36 265	4.6%	148	0.4%	1.8	1.25	[1.04, 1.50]	
	All women		Death from non-cardiovascular causes					
Pregnancy outcomes	*n*	%	*n*	%	rate	HR	CI	*P*
None	643 935	82.3%	4181	0.6%	4.5	1.00	[reference]	<0.001
PTD	31 132	4.0%	271	0.9%	6.4	1.44	[1.27, 1.63]	
SGA	33 311	4.3%	446	1.3%	8.1	1.66	[1.51, 1.83]	
PTD + SGA	5206	0.7%	87	1.7%	10.4	2.12	[1.72, 2.62]	
Pre-eclampsia	25 184	3.2%	155	0.6%	4.1	0.89	[0.76, 1.04]	
Pre-eclampsia + PTD	2662	0.3%	14	0.5%	4.3	1.05	[0.62, 1.78]	
Pre-eclampsia + SGA	2374	0.3%	25	1.1%	6.6	1.36	[0.92, 2.02]	
Pre-eclampsia + PTD + SGA	2218	0.3%	20	0.9%	6.5	1.48	[0.95, 2.29]	
Missing values	36 265	4.6%	577	1.6%	6.9	1.06	[0.97, 1.16]	

Maternal age and year of delivery were included in the models.
Rate is number of events per 10 000 years of observation.
CI, 95% confidence interval; HR, hazard ratio; PTD, preterm delivery; SGA, small-for-gestational-age offspring.

Discussion

The present study found that women delivering preterm or SGA offspring are at increased risk of early death from cardiovascular as well as non-cardiovascular causes. Women experiencing hypertensive disorders of pregnancy were at increased risk of subsequent death from cardiovascular causes, but not from non-cardiovascular causes. Interestingly, mild pre-eclampsia was associated with a slightly reduced risk of death from non-cardiovascular causes. Placental abruption was associated with death from all causes and non-cardiovascular causes, but not from cardiovascular causes. Stillbirth was associated with death from non-cardiovascular causes. Our findings highlight two principal issues: the subsequent shared cardiovascular mortality with a dose–response relationship, and a dis-

tinct increased risk of non-cardiovascular mortality, especially associated with preterm delivery and SGA.

Obstetric practice has changed over the 30 years of observation. For example, in Norway, Basso *et al*.[23] reported that the elective preterm delivery rate increased in pre-eclamptic pregnancies thereby lowering the stillbirth rate. We found no difference in maternal mortality after stillbirth in pre-eclamptic pregnancies. In our data, the combination of placental abruption and pre-eclampsia increased the risk of death from all causes, but abruption occurring in non-pre-eclamptic pregnancies was not linked to an increased risk of maternal death from cardiovascular causes. These findings imply a severity indicator of placental abruption in pre-eclamptic pregnancies and stillbirth in non-pre-eclamptic pregnancies.

A number of studies have previously investigated severe pregnancy complications and subsequent death.[17,18,24–30] Our findings are in accordance with these in that most of the studies found preterm delivery, pre-eclampsia and SGA offspring associated with an increased risk of subsequent death from cardiovascular causes, and these associations were found to be independent of each other.[17,24,31] This finding can also be seen as evidence of a severity effect, which enhances the biological plausibility of these pregnancy outcomes to cause later cardiovascular mortality. In other words, the primary manifestation in an individual woman's pregnancy differs, but eventually, with increasing severity, both maternal and fetal complications may occur. However, if these pregnancy complications are a part of the same underlying syndrome, they may represent different aspects of the pathophysiology.[5]

Pregnancy has been proposed as a 'stress test' for various chronic conditions,[32] but determining whether pregnancy complications are either mere markers of a woman's subsequent disease susceptibility, or are important modifiers of pathological processes, e.g. via accelerated systemic atherosclerosis[14] leading to cardiovascular morbidity, cannot be ascertained from the present study. In some cases, pregnancy complications are preceded by manifestations of the metabolic syndrome, which will predispose to later cardiovascular disease.[8,33,34] A possible relationship between the individual's genotype, pregnancy complications, and subsequent cardiovascular disease and death has yet to be discovered.[35]

The women in this cohort were quite young: the mean age at delivery was 27 years and the mean age at event or censoring was 42 years. In our initial stratified analyses, the younger population showed the greater mortality, i.e. the increased mortality was more pronounced in the earlier years following the pregnancy complication as compared with later follow-up, albeit not significantly. The increased mortality following pregnancy complications in this cohort is thus a marker of a severe cardiovascular vulnerability leading to premature death, most of the women being pre-menopausal; this also emphasises the need for caution when prescribing oral contraceptives to these women.[36,37]

The strengths and weaknesses of the study rest on the nature of the registry employed. We were able to assess parity and gestation, thus including only first deliveries and singletons to eliminate any effect modification from these variables. Also, women with any pre-pregnancy cardiovascular diseases and diabetes were excluded thereby ensuring a low-risk population. The ethnicity of the study cohort was homogenous given that the fertile female population consists of more than 91% ethnic Danish (Denmark's Statistical Agency); the social health care system in Denmark will also attenuate the effect from disparities in socio-economic status.

All these factors will diminish, but not eliminate, the potential bias of confounders such as smoking,[38] obesity[39] and socio-economic status, which we were not able to control for in the present study.[40] Smoking is a risk factor for SGA and placental abruption, but a protective factor for pre-eclampsia;[38,41] obesity is associated with hypertensive disorders of pregnancy and stillbirth;[4,39] and low socio-economic status is a risk factor for (spontaneous) preterm delivery and fetal growth restriction.[42] All these factors predispose to cardiovascular disease and death. Smoking appears to be a negative confounder in the association between hypertensive disorders of pregnancy and cardiovascular death, and a positive confounder in the association between SGA and cardiovascular death, i.e. adjusting for smoking will augment the estimates for death from cardiovascular causes following hypertensive disorders of pregnancy and attenuate the estimates for SGA. In the study by Kestenbaum *et al*.[43] the risk of cardiovascular morbidity imposed by smoking was comparable with that of hypertensive disorders of pregnancy; notably, the adjusted estimates did not differ from the unadjusted estimates when controlling for smoking. In our data, the observed protective effect of mild pre-eclampsia in death from non-

cardiovascular causes may also be attributed to the negative confounding effect of smoking.

Given the published estimates of the confounder effects of smoking, obesity and socio-economic status, it is likely that the most robust findings in the present study (the subsequent shared cardiovascular mortality with a dose–response relationship, and a distinct increased risk of non-cardiovascular mortality associated with preterm delivery and SGA) would remain significant. Nonetheless, it is possible that some of the increased mortality following pregnancy complications may be attributed to known risk factors.[44,45]

A potential weakness of this study, applicable to all registry-based studies, is the questionable validity of the exposures and end points: the ICD codes of the hypertensive disorders of pregnancy have been assessed to be very specific, but only moderately sensitive, with PPVs ranging from 56% to 100%. With a large reference group consisting of 85% of the population, the low sensitivity should have little impact on our findings. The moderate PPV of gestational hypertension (56%) could, however, reduce the association; also it is possible that the low sensitivity (10%) reflects a more severe form of gestational hypertension or imminent essential hypertension in the registry.

In conclusion, 14% of women giving birth to their first infant in Denmark have a pregnancy complication such as preterm delivery, SGA offspring and/or hypertensive disorders. We present evidence that this represents a subset of the population at increased risk of early death from cardiovascular causes; these women could perhaps benefit from life style modifications and possibly prophylactic therapies (e.g. statins). Women who deliver preterm or have an SGA offspring have an increased risk of non-cardiovascular death as well; this warrants further investigation into the risk factors and aetiology of these disorders.

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Conflict of interest

No potential conflict of interest relevant to this publication.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Diagnoses and ICD-8 and -10.

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