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Maternal Hypothyroidism and Documented History of Pregnancy Loss: A Registry Based Cross-Sectional Study of 66,279 Pregnancies in North-Eastern Iran

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Research Article

Keywords: Hypothyroidism, Pregnancy loss, Cross-sectional study, Electronic health records

Posted Date: November 20th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11574546/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Maternal hypothyroidism is a frequent endocrine disorder in pregnancy and has been linked to pregnancy loss, but most evidence comes from selected hospital populations with limited control for social and psychological factors. We examined whether a physician recorded diagnosis of hypothyroidism is associated with a documented history of pregnancy loss in a large primary care population.

Methods

Registry based cross-sectional study using the Sina Electronic Health Record System, which covers prenatal care in the primary health care network of Mashhad University of Medical Sciences (1 March 2017–20 September 2025). All pregnancies with a recorded diagnosis of hypothyroidism were enumerated (n = 33,079) and an approximately equal random sample of pregnancies without such a record was drawn from the same source population (n = 33,200; total N = 66,279). All included pregnancies ended in a delivery; the outcome was a documented history of pregnancy loss recorded in the maternal file. Because sampling was conditional on exposure and independent of the outcome, exposure specific prevalences, prevalence ratios and prevalence odds ratios are unbiased for the source population, whereas the pooled prevalence is not. Covariates were pre-specified on clinical and causal grounds and all were retained in the model. We report adjusted prevalence odds ratios (aPOR) from logistic regression and adjusted prevalence ratios (aPR) from modified Poisson regression with robust standard errors.

Results

A documented history of pregnancy loss was present in 3,578 of 33,079 women with recorded hypothyroidism (10.8%, 95% CI: 10.5–11.2) and in 2,145 of 33,200 women without (6.5%, 95% CI: 6.2–6.7): a prevalence difference of 4.4 percentage points (95% CI: 3.9–4.8) and a crude prevalence ratio of 1.67 (95% CI: 1.59–1.76). After adjustment, hypothyroidism remained associated with the outcome (aPOR = 1.61, 95% CI: 1.51–1.71; aPR = 1.50, 95% CI: 1.42–1.58). The strongest correlate was pregnancy number (aPOR = 12.22, 95% CI: 10.95–13.64 for a fourth or later pregnancy), followed by Iranian nationality (aPOR = 5.54, 95% CI: 4.29–7.16) and residence outside the metropolitan area (aPOR 1.41–2.23). Maternal age was positively associated with the outcome before adjustment but inversely associated after adjustment for pregnancy number (aPOR = 0.50, 95% CI: 0.41–0.61 for women older than 40 years). Depression (aPOR = 1.18), recorded obesity (aPOR = 1.20) and genitourinary disease (aPOR = 1.37) were also independently associated, whereas a positive domestic-violence screen, anxiety, diabetes, hypertension and a history of cancer were not.

Conclusions

Recorded maternal hypothyroidism was associated with a roughly 50% higher prevalence of documented pregnancy loss. Because the registry records neither thyroid function values, antibody status and levothyroxine treatment, nor the timing of the diagnosis relative to the loss, the analysis cannot establish temporality, distinguish overt from subclinical disease, or separate a biological effect from more complete documentation in women under closer follow up. The findings support the recording of thyroid function values and treatment in structured prenatal fields so that these questions can be addressed directly, and they should not be used to justify a particular screening or treatment policy.

1. Introduction

Hypothyroidism is one of the most common chronic conditions in pregnant women, and is classified as overt (clinical) or subclinical (1). Thyroid dysfunction is the second most common endocrine disorder of pregnancy after diabetes (2). Overt hypothyroidism affects an estimated 0.3–0.5% of pregnancies and subclinical hypothyroidism 2–3% (4), although reported figures vary widely with the diagnostic threshold applied. In Iran, a national meta-analysis reported thyroid dysfunction in 18.10% of pregnant women, with hypothyroidism the most common form (13.01%: 1.35% clinical and 11.90% subclinical) (3).

Iodine deficiency and excess are major causes of maternal hypothyroidism worldwide; where iodine intake is adequate, chronic autoimmune thyroiditis is the principal cause (5). Other contributors include iron deficiency, previous thyroidectomy, radioactive iodine therapy, head and neck irradiation, inadequately treated hypothyroidism, and thyroid dysgenesis (6). Maternal hypothyroidism has been linked to preeclampsia, gestational hypertension, gestational diabetes, placental abruption, low birth weight, preterm birth, intrauterine fetal demise, impaired neurodevelopment and pregnancy loss (7–13), although the strength of the association with pregnancy loss remains contested and estimates differ by diagnostic criteria, population and study design (14, 15).

Large routine health care databases can contribute to this literature because they cover whole care networks rather than selected hospital populations and allow simultaneous adjustment for medical, psychological and socioeconomic factors. They also have a characteristic weakness: they record what clinicians document, not what is biologically present, and the fields available determine which questions can be answered. The aim of the present study was to quantify the association between a physician recorded diagnosis of maternal hypothyroidism and a documented history of pregnancy loss in the prenatal records of an entire primary health-care network, and to report that association on both the relative and the absolute scale while being explicit about what the data source can and cannot support.

2. Methods

2.1 Design, setting and sampling

This was a registry based cross-sectional study using routinely collected data from the Sina Electronic Health Record System (16), which supports prenatal care in the primary health care network affiliated with Mashhad University of Medical Sciences, north eastern Iran, between 1 March 2017 and 20 September 2025. Eligible records were pregnancies registered for routine prenatal care during this period with a completed delivery record.

The eligible source population comprised 543,186 pregnancies. Within it, all pregnancies with a physician-recorded diagnosis of hypothyroidism were included by complete enumeration (n = 33,079, 6.1% of the source population), and pregnancies with no record of hypothyroidism were sampled at random, without replacement, in an approximately 1:1 ratio (n = 33,200 of 510,107, a sampling fraction of 6.5%), giving 66,279 analysed records. Two consequences of this scheme are stated explicitly. First, the proportion of exposed records in the analytic sample (49.9%) is a feature of the design and carries no information about the prevalence of hypothyroidism in the population; the pooled outcome prevalence (8.6%) is likewise not a population estimate. Second, because sampling was conditional on exposure and independent of the outcome, the outcome prevalence within each exposure group, and therefore the prevalence ratio, prevalence difference and prevalence odds ratio, are unbiased for the source population and no sampling weights are required. Participant flow is shown in Fig. 1.

2.2 Outcome definition

The outcome was a documented history of pregnancy loss, recorded as a structured field in the maternal prenatal file. Every record analysed also contains a completed delivery record with a recorded birth weight (mean 3.16 kg); the index pregnancies therefore ended in delivery, and the outcome refers to a loss in an earlier pregnancy. This is the reason the study is analysed as cross-sectional rather than as a cohort: the outcome is a state recorded in the maternal history at the time of the index pregnancy, not an event observed during follow up. The registry does not record the gestational age at which the loss occurred, nor whether the loss was spontaneous, therapeutic or induced and the field does not distinguish one loss from several. The system holds a second, broader field recording whether any previous abortion was registered, which was positive in 16,431 records (24.8%) and captures a wider range of pregnancy terminations; agreement between the two fields is partial and is tabulated in Supplementary Table S6. Because the choice of field is a measurement decision rather than a settled one, the main analysis was repeated with the broader field as the outcome (Section 3.5).

2.3 Exposure definition

The exposure was a physician recorded diagnosis of hypothyroidism in the structured prenatal record (ICD-10 category E03.x). Diagnoses are made by the attending physician under the national Integrated Maternal Health Care programme of the Iranian Ministry of Health, which is the protocol operating throughout the primary health care network (29). The programme requires thyroid stimulating hormone (TSH) measurement before pregnancy or, where no valid result from the preceding year is available, at the first prenatal visit; a TSH above 3.9 mIU/L is classified as hypothyroidism and prompts referral for specialist assessment and management, with free thyroxine measured when TSH is abnormal. The

guideline has been revised during the study period, most recently in 2023, and the operational threshold has varied slightly between editions. The registry stores the diagnosis but not the underlying laboratory values, so overt and subclinical disease cannot be separated; it does not record the date of diagnosis relative to conception or to the earlier pregnancy in which the loss occurred; and levothyroxine prescriptions, doses, timing and adherence are not retrievable, so treated and untreated women cannot be distinguished. Thyroid peroxidase antibody status is not measured in the programme. The exposure should therefore be read throughout as 'recorded diagnosis of hypothyroidism', encompassing overt and subclinical, treated and untreated disease.

2.4 Covariates

Covariates were prespecified on clinical and causal grounds using the simplified directed acyclic graph in Fig. 2, and not by their statistical significance. The set comprised maternal age (< 20, 20–30, 30–40, > 40 years), pregnancy number, nationality, place of residence (metropolis, small city, village, peri-urban), maternal education, maternal occupation, domestic violence measured with the HITS screening score, depression, anxiety, recorded obesity, diabetes, hypertension, history of cancer and genitourinary disease. All were retained in the final model irrespective of their p-values, which is why non significant categories appear in Table 2.

Three measurement details affect how the corresponding estimates should be read and are therefore reported here rather than in the limitations. First, residence categories follow the coding of the source system, in which 'village' denotes rural settlements and 'peri-urban' the informal settlements on the margin of the metropolitan area. Second, domestic violence was defined from the HITS screening score itself (17), which is administered by the midwife during prenatal counselling and recorded as a separate structured field. HITS has four items scored 1 to 5, giving a valid range of 4 to 20, and a total above 10 was classified as a positive screen. A valid score was available for 42,724 records (64.5%): 10,685 records (16.1%) had no score and a further 12,870 (19.4%) held a value outside the valid range, almost all of them zero, which indicates that the instrument was not administered. These records form a separate 'not screened or invalid' category rather than being discarded, so that the analytic sample remains complete. Third, obesity is the clinician-recorded diagnosis field in the prenatal record. Smoking, alcohol and substance use, infertility treatment, iodine status and medications affecting thyroid function are not collected by the system.

A feature of the data source that applies to the exposure and to every comorbidity covariate should be stated before the results are read. In this system a condition is stored as present only when a clinician has recorded the diagnosis during a care episode. A woman who was investigated and found not to have the condition, and a woman who was never investigated for it, are both stored in the same way, as not having the condition, and the extract does not distinguish the two. Coverage of the primary health care network is high and most pregnancies pass through the routine screening schedule, which limits how far undocumented disease can accumulate, but the fields nonetheless record documented disease rather than true disease status. For the exposure this means that women with undiagnosed or unrecorded hypothyroidism are counted as unexposed, which would ordinarily attenuate the association; for the

covariates it means residual confounding by conditions that were present but never recorded. Data completeness for every variable is reported in Supplementary Table S4.

2.5 Statistical analysis

All analyses were performed in Stata version 16 (StataCorp, College Station, TX, USA). Distributions were described by outcome status and compared with the chi-square test; the outcome of every analysis was the documented history of pregnancy loss. Unadjusted prevalence odds ratios were obtained from single-variable logistic models and adjusted estimates from a single multivariable logistic model containing all pre-specified covariates. Because the outcome is not rare, odds ratios overstate prevalence ratios; adjusted prevalence ratios were therefore estimated directly with modified Poisson regression using robust (Huber–White sandwich) standard errors, and absolute prevalences with exact binomial confidence intervals, the prevalence difference and the crude prevalence ratio are also reported (Table 3).

Multicollinearity was assessed with variance inflation factors (maximum 6.54, for the maternal-age indicators; all others below 2). Calibration was assessed with the Hosmer–Lemeshow test ($\chi^2 = 32.52$, df = 8, $p = 0.0001$) and discrimination with the c-statistic (0.765). We report the Hosmer–Lemeshow result as evidence of imperfect fit, while noting that with 66,279 observations the test detects departures from perfect calibration that are of little practical consequence. Three further analyses were prespecified: an expanded model adding exact maternal age, anaemia, food insecurity, a recorded psychological-stress flag and a lifestyle score (complete in 57,566 records); a subgroup analysis restricted to first pregnancies; and a repetition of the main model with the alternative outcome field. Full coefficients, standard errors, z values and p values for the main logistic model, the modified Poisson model and the expanded model are reported in Supplementary Tables S1, S2 and S3 respectively.

2.6 Ethics

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (2013 revision) and approved by the Ethics Committee of Mashhad University of Medical Sciences (approval code IR.MUMS.FHMPM.REC.1403.218).

3. Results

3.1 Sample and outcome

Of 66,279 records analysed, 33,079 carried a recorded diagnosis of hypothyroidism and 33,200 did not; 5,723 records (8.6% of the analytic sample, which is a function of the sampling design) carried a documented history of pregnancy loss. Distributions are shown in Table 1 and all unadjusted associations were significant at $p < 0.001$. Because exposed pregnancies were enumerated in full, the prevalence of a recorded diagnosis of hypothyroidism in the source population can be estimated directly: 33,079 of 543,186 pregnancies, or 6.1%.

3.2 Hypothyroidism and pregnancy loss

A documented history of pregnancy loss was present in 10.8% (95% CI: 10.5–11.2) of women with recorded hypothyroidism and 6.5% (95% CI: 6.2–6.7) of women without, a prevalence difference of 4.4 percentage points (95% CI: 3.9–4.8) and a crude prevalence ratio of 1.67 (95% CI: 1.59–1.76). After adjustment for all pre-specified covariates the association persisted (aPOR = 1.61, 95% CI: 1.51–1.71, $p < 0.001$), and the directly estimated adjusted prevalence ratio was 1.50 (95% CI: 1.42–1.58). All measures are given in Table 3.

3.3 Other correlates

Pregnancy number showed the strongest association: relative to a first pregnancy, the adjusted odds increased from 3.19 (95% CI: 2.87–3.56) for a second to 12.22 (95% CI: 10.95–13.64) for a fourth or later pregnancy. This is expected rather than informative, since a woman's pregnancy count is itself a consequence of earlier pregnancy outcomes, including losses; the estimate is reported for completeness and is not interpreted as an effect.

Maternal age behaved differently before and after adjustment. Unadjusted, the odds rose monotonically with age (up to 2.19, 95% CI: 1.83–2.62, in women older than 40 years); adjusted for pregnancy number and the remaining covariates, the association reversed (0.50, 95% CI: 0.41–0.61). The reversal is a consequence of conditioning on pregnancy number: among women at the same pregnancy number, older age implies a longer interval without additional pregnancies. Both estimates are reported, since the unadjusted and adjusted quantities answer different questions.

Iranian nationality was strongly associated with the outcome (aPOR = 5.54, 95% CI: 4.29–7.16), which is implausible as a biological effect and is better explained by documentation: among non-Iranian women, predominantly Afghan migrants, only 1.5% of records carried a documented history of pregnancy loss, consistent with later registration and less complete maternal history. Residence outside the metropolitan area was associated with a higher prevalence (small city aPOR = 2.23, village 1.99, peri-urban 1.41). Depression (1.18, 95% CI: 1.08–1.28), recorded obesity (1.20, 95% CI: 1.07–1.34) and genitourinary disease (1.37, 95% CI: 1.27–1.49) remained associated after adjustment. A positive HITS screen (0.69, 95% CI: 0.31–1.53), anxiety (1.04, 95% CI: 0.94–1.14), diabetes (1.15, 95% CI: 0.94–1.41), hypertension (0.95, 95% CI: 0.80–1.13) and a history of cancer (0.92, 95% CI: 0.72–1.17) were not independently associated with the outcome. Only 95 records had a HITS score above 10 and only 7 of these carried the outcome, so this estimate is too imprecise to exclude either a meaningful association or none.

Education and occupation showed the same pattern. Unadjusted, education above diploma level was associated with a lower prevalence of documented loss than illiteracy or primary education (0.55, 95% CI: 0.50–0.60), and employed and selfemployed women had lower odds than housewives (0.70 for both). Neither gradient survived adjustment: relative to illiterate or primary educated women the adjusted odds were 1.14 for diploma-level and 1.16 for above diploma education, students had higher adjusted odds than housewives (1.31, 95% CI: 1.16–1.48), and selfemployed and employed women did not differ

significantly. The apparent socioeconomic gradient in these data is therefore attributable to residence, nationality and pregnancy number rather than to education or employment themselves.

3.4 Expanded model

In the expanded model (57,566 records with a complete lifestyle score), the association with hypothyroidism was unchanged (aPOR = 1.66 (1.56–1.77)). Exact maternal age was inversely associated with the outcome (0.95 (0.95–0.96) per year), anaemia was borderline (1.11 (1.00–1.23)) and a recorded psychological stress flag was inversely associated (0.82 (0.73–0.92)), the last most plausibly reflecting who is screened rather than a protective effect. Food insecurity showed no association.

3.5 Sensitivity analyses

Restricted to first pregnancies (n = 23,949, 518 outcome records), the association with hypothyroidism was stronger (aPOR = 3.17 (2.56–3.91)); this subgroup should be read with caution, since a documented history of loss in a first recorded pregnancy implies either a loss occurring before first registration with the network or an error in data entry. Using the alternative registry field for previous abortion as the outcome (16,431 records positive), the association was attenuated but persisted (aPOR = 1.44 (1.38–1.51)). The difference between the two estimates indicates that the magnitude of the association depends on which registry field is used to define pregnancy loss.

Table 1
Documented history of pregnancy loss by maternal characteristics (N = 66,279). Row percentages.

Variable	Category	No history n (%)	History of loss n (%)	p
Recorded hypothyroidism	No	31,055 (93.5)	2,145 (6.5)	< 0.001
	Yes	29,501 (89.2)	3,578 (10.8)	
Maternal age (years)	< 20	3,219 (95.2)	162 (4.8)	< 0.001
	20–30	25,850 (91.6)	2,372 (8.4)	
	30–40	26,195 (90.9)	2,607 (9.1)	
	> 40	5,292 (90.1)	582 (9.9)	
Pregnancy number	First	23,431 (97.8)	518 (2.2)	< 0.001
	Second	15,520 (92.7)	1,214 (7.3)	
	Third	11,380 (87.4)	1,639 (12.6)	
	Fourth or more	10,225 (81.3)	2,352 (18.7)	
Nationality	Non-Iranian	4,189 (98.5)	63 (1.5)	< 0.001
	Iranian	56,367 (90.9)	5,660 (9.1)	
Place of residence	Metropolis	17,414 (95.9)	736 (4.1)	< 0.001
	Small city	10,201 (87.7)	1,435 (12.3)	
	Village	16,513 (87.6)	2,337 (12.4)	
	Peri-urban (city margin)	16,428 (93.1)	1,215 (6.9)	
Maternal education	Illiterate/primary	14,589 (90.6)	1,513 (9.4)	< 0.001
	Diploma	32,683 (90.4)	3,458 (9.6)	
	Above diploma	13,284 (94.6)	752 (5.4)	
Maternal occupation	Housewife	53,197 (91.2)	5,151 (8.8)	< 0.001
	Self-employed	1,145 (93.6)	78 (6.4)	
	Employee	1,743 (93.7)	118 (6.3)	
	Student	4,471 (92.2)	376 (7.8)	

Variable	Category	No history n (%)	History of loss n (%)	p
Domestic violence (HITS)	HITS 4–10	38,439 (90.2)	4,190 (9.8)	< 0.001
	HITS > 10	88 (92.6)	7 (7.4)	
	Not screened / invalid score	22,029 (93.5)	1,526 (6.5)	
Depression	No	55,673 (91.7)	5,007 (8.3)	< 0.001
	Yes	4,883 (87.2)	716 (12.8)	
Anxiety	No	56,139 (91.6)	5,154 (8.4)	< 0.001
	Yes	4,417 (88.6)	569 (11.4)	
Anaemia	No	56,973 (91.7)	5,185 (8.3)	< 0.001
	Yes	3,583 (86.9)	538 (13.1)	
Recorded psychological stress	No	56,094 (91.4)	5,309 (8.6)	0.729
	Yes	4,462 (91.5)	414 (8.5)	
Food insecurity	No	56,342 (91.3)	5,368 (8.7)	0.033
	Yes	4,214 (92.2)	355 (7.8)	
Obesity (recorded diagnosis)	No	57,561 (91.5)	5,332 (8.5)	< 0.001
	Yes	2,995 (88.5)	391 (11.5)	
Diabetes	No	59,722 (91.4)	5,601 (8.6)	< 0.001
	Yes	834 (87.2)	122 (12.8)	
Hypertension	No	59,394 (91.5)	5,549 (8.5)	< 0.001
	Yes	1,162 (87.0)	174 (13.0)	
History of cancer	No	60,020 (91.4)	5,641 (8.6)	< 0.001
	Yes	536 (86.7)	82 (13.3)	
Genitourinary disease	No	55,333 (92.1)	4,753 (7.9)	< 0.001

Variable	Category	No history n (%)	History of loss n (%)	p
	Yes	5,223 (84.3)	970 (15.7)	

Percentages are row percentages within each category. Residence categories follow the coding of the source system. p-values are from chi-square tests of the unadjusted association with the outcome.

Table 2
Unadjusted and adjusted associations with a documented history of pregnancy loss (N = 66,279).

Variable	Category	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p	Adjusted PR
Recorded hypothyroidism	*No (reference)*	1.00	—	1.00	—	1.00
	Yes	1.76 (1.66–1.86)	< 0.001	1.61 (1.51–1.71)	< 0.001	1.50 (1.42–1.58)
Maternal age (years)	*< 20 (reference)*	1.00	—	1.00	—	1.00
	20–30	1.82 (1.55–2.15)	< 0.001	0.88 (0.74–1.05)	0.144	0.88 (0.76–1.03)
	30–40	1.98 (1.68–2.33)	< 0.001	0.54 (0.45–0.65)	< 0.001	0.59 (0.50–0.69)
	> 40	2.19 (1.83–2.62)	< 0.001	0.50 (0.41–0.61)	< 0.001	0.55 (0.46–0.66)
Pregnancy number	*First (reference)*	1.00	—	1.00	—	1.00
	Second	3.54 (3.19–3.93)	< 0.001	3.19 (2.87–3.56)	< 0.001	3.02 (2.72–3.35)
	Third	6.51 (5.89–7.21)	< 0.001	6.59 (5.92–7.35)	< 0.001	5.70 (5.12–6.34)
	Fourth or more	10.40 (9.43–11.48)	< 0.001	12.22 (10.95–13.64)	< 0.001	9.45 (8.49–10.52)
Nationality	*Non-Iranian (reference)*	1.00	—	1.00	—	1.00
	Iranian	6.68 (5.20–8.58)	< 0.001	5.54 (4.29–7.16)	< 0.001	4.94 (3.84–6.37)
Place of residence	*Metropolis (reference)*	1.00	—	1.00	—	1.00
	Small city	3.33 (3.04–3.65)	< 0.001	2.23 (2.02–2.46)	< 0.001	2.03 (1.86–2.21)

Variable	Category	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p	Adjusted PR
	Village	3.35 (3.07–3.65)	< 0.001	1.99 (1.81–2.19)	< 0.001	1.84 (1.69–2.01)
	Peri-urban (city margin)	1.75 (1.59–1.92)	< 0.001	1.41 (1.28–1.55)	< 0.001	1.37 (1.25–1.50)
Maternal education	*Illiterate/primary (reference)*	1.00	—	1.00	—	1.00
	Diploma	1.02 (0.96–1.09)	0.537	1.14 (1.06–1.22)	< 0.001	1.11 (1.05–1.18)
	Above diploma	0.55 (0.50–0.60)	< 0.001	1.16 (1.05–1.29)	0.005	1.13 (1.03–1.23)
Maternal occupation	*Housewife (reference)*	1.00	—	1.00	—	1.00
	Self-employed	0.70 (0.56–0.89)	0.003	0.97 (0.77–1.24)	0.830	0.98 (0.79–1.21)
	Employee	0.70 (0.58–0.84)	< 0.001	1.18 (0.96–1.44)	0.116	1.14 (0.96–1.36)
	Student	0.87 (0.78–0.97)	0.011	1.31 (1.16–1.48)	< 0.001	1.28 (1.15–1.41)
Domestic violence (HITS)	*HITS 4–10 (reference)*	1.00	—	1.00	—	1.00
	HITS > 10	0.73 (0.34–1.58)	0.423	0.69 (0.31–1.53)	0.360	0.73 (0.37–1.44)
	Not screened / invalid score	0.64 (0.60–0.68)	< 0.001	0.98 (0.92–1.05)	0.582	0.98 (0.93–1.03)
Depression	*No (reference)*	1.00	—	1.00	—	1.00
	Yes	1.63 (1.50–1.77)	< 0.001	1.18 (1.08–1.28)	< 0.001	1.14 (1.06–1.22)
Anxiety	*No (reference)*	1.00	—	1.00	—	1.00

Variable	Category	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p	Adjusted PR
	Yes	1.40 (1.28–1.54)	< 0.001	1.04 (0.94–1.14)	0.432	1.03 (0.95–1.12)
Obesity (recorded diagnosis)	*No (reference)*	1.00	—	1.00	—	1.00
	Yes	1.41 (1.26–1.57)	< 0.001	1.20 (1.07–1.34)	0.002	1.16 (1.06–1.27)
Diabetes	*No (reference)*	1.00	—	1.00	—	1.00
	Yes	1.56 (1.29–1.89)	< 0.001	1.15 (0.94–1.41)	0.171	1.12 (0.95–1.33)
Hypertension	*No (reference)*	1.00	—	1.00	—	1.00
	Yes	1.60 (1.36–1.88)	< 0.001	0.95 (0.80–1.13)	0.598	0.96 (0.84–1.11)
History of cancer	*No (reference)*	1.00	—	1.00	—	1.00
	Yes	1.63 (1.29–2.06)	< 0.001	0.92 (0.72–1.17)	0.493	0.93 (0.76–1.14)
Genitourinary disease	*No (reference)*	1.00	—	1.00	—	1.00
	Yes	2.16 (2.01–2.33)	< 0.001	1.37 (1.27–1.49)	< 0.001	1.29 (1.21–1.37)

OR = prevalence odds ratio; PR = prevalence ratio from modified Poisson regression with robust standard errors; CI = confidence interval. Crude estimates come from single-variable models; adjusted estimates come from a single multivariable model containing every variable shown. Full coefficients and standard errors are given in Supplementary Tables S1 and S2.

Table 3
Absolute and relative measures for recorded hypothyroidism.

Measure	Estimate (95% CI)
Prevalence of documented previous pregnancy loss, exposed (n = 33,079)	10.8% (10.5–11.2)
Prevalence, unexposed (n = 33,200)	6.5% (6.2–6.7)
Crude prevalence difference	4.4 percentage points (3.9–4.8)
Crude prevalence ratio	1.67 (1.59–1.76)
Crude prevalence odds ratio	1.76 (1.66–1.86)
Adjusted prevalence odds ratio (logistic)	1.61 (1.51–1.71)
Adjusted prevalence ratio (modified Poisson, robust SE)	1.50 (1.42–1.58)

Prevalences, the prevalence difference and the prevalence ratio are valid for the source population because sampling was conditional on exposure and independent of the outcome. Exact binomial confidence intervals are given for prevalences.

4. Discussion

In 66,279 prenatal records from an entire primary health care network, women with a recorded diagnosis of hypothyroidism were about half as likely again to have a documented history of pregnancy loss as women without such a record (10.8% versus 6.5%; adjusted prevalence ratio 1.50). The association was robust to adjustment for demographic, socioeconomic, psychosocial and medical covariates, to the addition of exact maternal age, anaemia, food insecurity, psychological stress and a lifestyle score, and, in attenuated form, to the use of an alternative registry field for pregnancy loss.

The direction of this association is consistent with the literature, although published effect sizes vary widely with the population and the definition of thyroid dysfunction. In women with recurrent pregnancy loss, the combination of overt hypothyroidism and positive thyroid autoantibodies has been reported to quadruple the odds of loss before 20 weeks (OR 4.04, 95% CI: 2.08–7.96), whereas subclinical hypothyroidism with positive antibodies was not significantly associated (18). A meta-analysis of nine studies found untreated subclinical hypothyroidism associated with miscarriage (RR 1.90, 95% CI: 1.59–2.27), with no difference between treated subclinical hypothyroidism and euthyroid women (RR 1.14), and a higher risk when thyroid autoimmunity coexisted (RR 2.47) (19). A recent bidirectional Mendelian randomisation analysis found a positive but very small association between genetically predicted hypothyroidism and spontaneous abortion (OR 1.024, 95% CI: 1.005–1.043) and no association with recurrent loss (23), which suggests that the larger associations seen in observational data, including ours, reflect a combination of a modest causal contribution, confounding by autoimmunity and severity, and differential ascertainment. Subclinical hypothyroidism has also been associated with hypertensive

disorders of pregnancy in a meta-analysis of 22 studies (OR 1.54, 95% CI: 1.21–1.96) (25). Clinical guidance remains correspondingly cautious: thyroid dysfunction is recognised as a consideration in the assessment of recurrent pregnancy loss (20), while current guidance on managing thyroid disorders in pregnancy emphasises that the evidence supporting treatment of milder abnormalities is limited (21), and observational series of feto maternal outcomes in hypothyroid pregnancies report the same direction of association without resolving the question of treatment benefit (22). Persistent isolated maternal hypothyroxinemia in early pregnancy has been linked to adverse obstetric outcomes (24), and treatment timing and antibody status appear to modify the effect of therapy (26).

Our estimate cannot be interpreted causally, and the reasons are specific rather than generic. The design is cross-sectional: both the diagnosis and the history of loss are recorded in the same prenatal file, and the registry does not record when the hypothyroidism was diagnosed relative to the pregnancy that was lost. A woman who experiences a pregnancy loss is likely to undergo more extensive investigation afterwards, including thyroid function testing, so part of the association may run from loss to diagnosis rather than the reverse. With these data this possibility cannot be excluded; it can be resolved only by linking the date of the thyroid diagnosis to the date of each loss, which is the analysis we propose next.

A second and partly opposing mechanism is documentation. Women with a chronic diagnosis attend more often and have a fuller maternal history recorded, so a previous loss is more likely to be documented in the exposed group. The nationality finding shows how strong this effect can be in these data: a fivefold difference between Iranian and non-Iranian women is not plausibly biological. Working against both mechanisms, women whose hypothyroidism is never diagnosed are counted as unexposed, which attenuates the association. The net direction of these biases cannot be determined with the present data, and the point estimate should be read as an upper bound on any causal effect rather than as a measure of one.

The reversal of the age association after adjustment deserves comment because it is easy to misread. Older women more often have a documented loss simply because they have had more pregnancies; once pregnancy number is held constant, the residual association is inverse. Neither estimate answers the clinically relevant question of how age affects the risk of loss in a given pregnancy, which requires pregnancy-level incidence data rather than a maternal-history field. The same caution applies to pregnancy number itself, which is partly determined by previous outcomes.

The psychosocial findings should be read as findings about documentation. A positive HITS screen was recorded in 95 of 66,279 records, which is far below any plausible prevalence of intimate partner violence in Iran, and more than a third of records had no valid HITS score at all. The screen was not associated with the outcome after adjustment, but with seven outcome events among screened-positive women this tells us more about the reach of the screening programme than about violence itself. Depression remained associated, consistent with reports linking psychiatric disorders to pregnancy loss (27, 28), but with a diagnosis-based exposure the possibility that depression is documented more often after a loss cannot be separated from a contribution in the other direction.

Strengths and limitations

The main strengths are the size and coverage of the data source, which includes an entire primary-care network rather than a selected hospital population, the complete enumeration of exposed pregnancies, the availability of socioeconomic and psychosocial variables rarely present in registry studies, and the reporting of the association on the absolute as well as the relative scale.

The limitations are substantial. The outcome is a documented history of pregnancy loss in a maternal record rather than an incident, gestational age defined miscarriage; the gestational age, the type of loss and the number of losses are unknown, and two registry fields intended to capture previous loss agree only partially. The design cannot establish temporality between the diagnosis and the loss. The exposure is a recorded diagnosis with no laboratory values, no antibody status and no treatment data, so overt and subclinical disease and treated and untreated women are analysed together. Established confounders including smoking, substance use, infertility treatment and iodine status are not collected. Comorbidity fields, and the exposure field itself, store the absence of a record as absence of disease: a woman who was investigated and not diagnosed and a woman who was never investigated are indistinguishable in the extract, so what is analysed throughout is documented rather than true disease status. High coverage of the primary health-care network limits but does not remove this problem, and its expected effects run in opposite directions, attenuating the exposure association while leaving residual confounding by undocumented comorbidity. The HITS screen was not completed, or produced an out-of-range value, for more than a third of records, which leaves the violence estimate uninformative, and the lifestyle score is missing for one record in eight, restricting the expanded model. Model calibration was imperfect by the Hosmer–Lemeshow criterion, although discrimination was reasonable. Finally, the exposure-stratified sampling means that neither the prevalence of hypothyroidism nor the overall prevalence of pregnancy loss in this sample can be generalised to the population.

5. Conclusion

In a large primary-care population, a recorded diagnosis of maternal hypothyroidism was associated with a roughly 50% higher prevalence of documented pregnancy loss, independent of a wide range of demographic, socioeconomic, psychosocial and medical characteristics. The association is consistent with the published literature in direction, but its magnitude cannot be interpreted as a causal effect: the design is cross-sectional, the timing of the diagnosis relative to the loss is unknown, disease severity and treatment are not recorded, and documentation intensity differs systematically between the groups being compared. The practical implication is one for data systems rather than for clinical policy. Recording thyroid-function values, antibody results and levothyroxine prescriptions in structured prenatal fields, together with the gestational age and type of each pregnancy loss, would allow the questions that matter clinically to be answered directly in this population. Until then, these findings should be read as evidence of an association worth investigating, and not as a basis for changing screening or treatment practice.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki (2013 revision). Ethical approval was obtained from Mashhad University of Medical Sciences (approval code IR.MUMS.FHMPM.REC.1403.218). Written informed consent was obtained from all participants before their inclusion in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Funding

This research was supported by a grant from Mashhad University of Medical Sciences (grant number 4031647).

Authors' contributions

MN is the principal investigator and research leader. AM and EM designed the study, drafted the manuscript and analysed the data. MS and SA contributed to the conception, design, data interpretation and revision of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Use of artificial intelligence

Artificial intelligence assisted tools were used during the preparation of this manuscript for language editing, for checking internal consistency between the text, the tables and the figures, and for reviewing the analysis code and statistical output. Every stage was checked by the authors: all analyses were verified against the source data, and all text was read, corrected and approved by the authors. Artificial intelligence was not used to generate scientific content, results or conclusions, does not meet the

criteria for authorship, and is not listed as an author. The authors take full responsibility for the accuracy and integrity of the manuscript, including all data, analyses and interpretations presented.

Reporting guideline

The study is reported in accordance with the STROBE statement for cross-sectional studies; the completed checklist is provided as Supplementary Table S5 and participant flow is shown in Figure 1.

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Figures

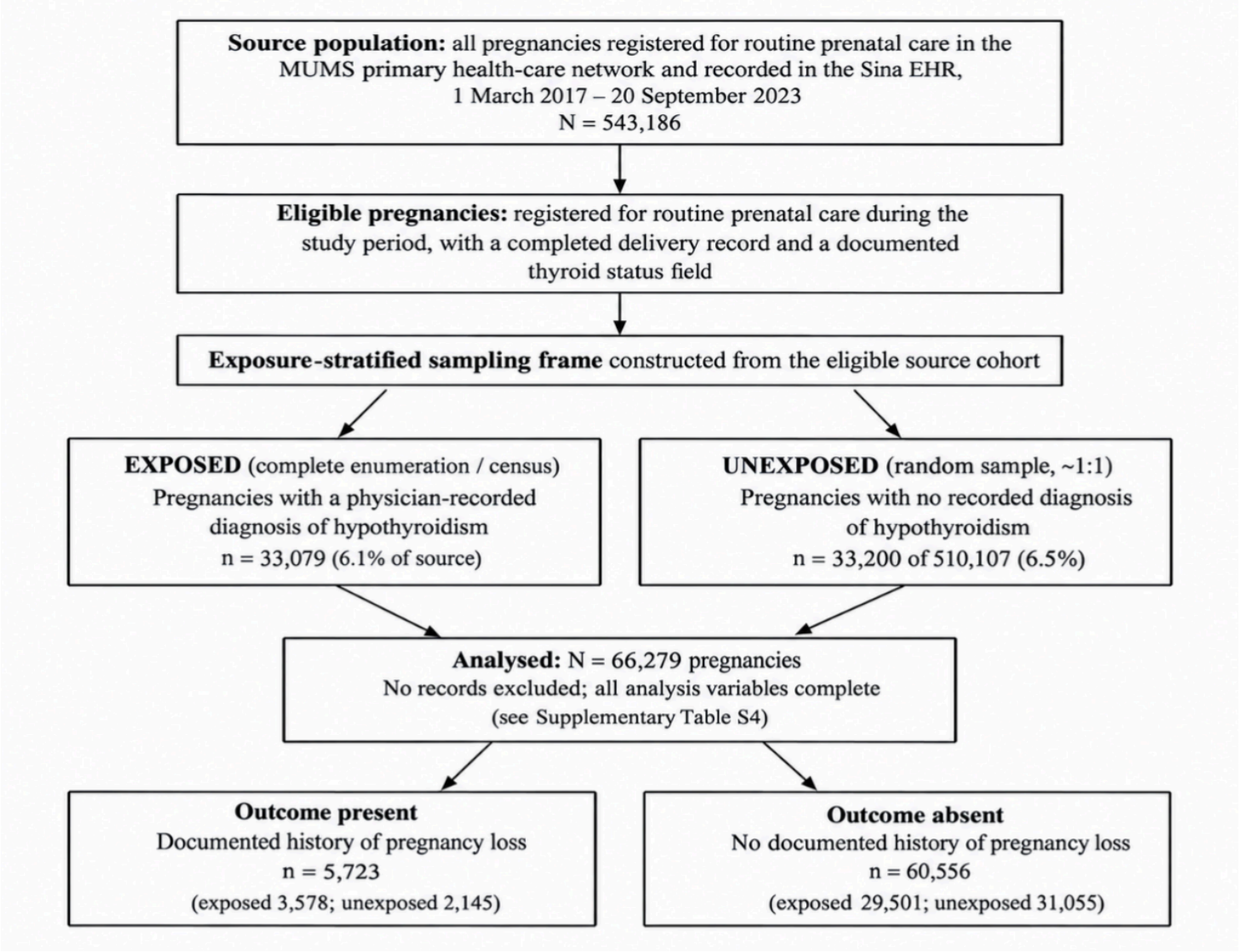


Figure 1

Participant flow (STROBE).

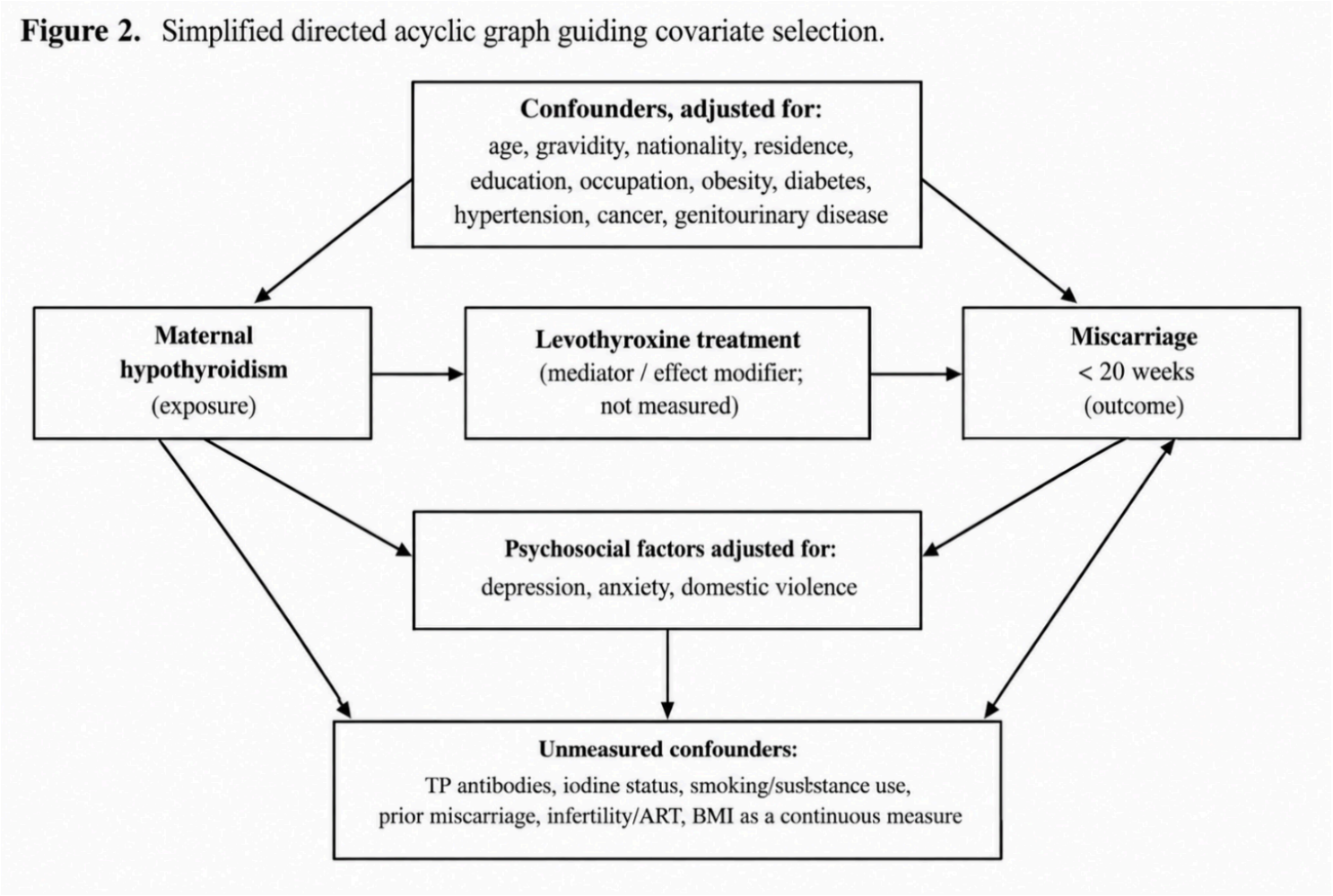


Figure 2

Simplified directed acyclic graph used to pre-specify covariates. Levothyroxine treatment lies between exposure and outcome and is not measured; the unmeasured confounders shown are the main sources of residual confounding.