



Incident anaemia as a marker of cancer and all-cause mortality: evidence from 380 114 adults in the population-based Stockholm Early Detection of Cancer Study (STEADY-CAN) cohort

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ABSTRACT

Objective Anaemia is common in healthcare and may indicate undiagnosed cancer. Despite this, evidence regarding risk estimates informing clinical decision-making remains limited, particularly regarding haemoglobin dynamics and the role of mean corpuscular volume (MCV). We aimed to quantify the 18-month risks of incident cancer (IC) and all-cause mortality (ACM) following incident anaemia (IA), and to examine how MCV modifies these risks.

Methods and analysis Population-based, age- and sex-matched cohort study. The study used the Stockholm Early Detection of Cancer Study (STEADY-CAN), covering almost all adults residing in Stockholm County, Sweden, during 2011–2021. STEADY-CAN links laboratory tests with national registers, capturing healthcare use, diagnoses, cancer outcomes and prescribed medications.

We included 190 057 adults with IA and 190 057 age- and sex-matched non-anaemic controls from the STEADY-CAN cohort. Eligible individuals were ≥18 years old, cancer-free, had ≥2 Hb measurements during 2011–2020 and a concurrent MCV value at the IA date. IA was defined as the first Hb value from 2012 onwards below 130 g/L in men or 120 g/L in women after prior normal values.

Sex-stratified adjusted piecewise competing-risks multi-state Cox regression models were used, with separate HRs for IA during 0–3, 3–6, 6–12 and 12–18 months of follow-up. The main outcome measures were IC and ACM during the 18-month follow-up.

Results IC occurred in 6.2% of male and 2.8% of female IA cases, compared with 2.4% and 1.1% of controls. Corresponding ACM rates were 7.4% and 4.0% in IA cases versus 2.5% and 1.7% in controls. IA implied a 9.17-fold higher IC risk and 8.50-fold higher ACM risk among men during 0–3 months of follow-up, with 8.25- and 6.14-fold higher risks among women (all $p < 0.001$). These risks decreased over time but were still significant for both sexes at 6–12 months of follow-up for IC and 12–18 months of follow-up for ACM. Microcytosis was linked to the highest IC risk, particularly for digestive and haematological cancers, whereas macrocytosis was more strongly associated with ACM.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Anaemia is common in routine care and though it may signal undiagnosed cancer, there might be multiple other possible causes as well. Existing evidence is mainly derived from small or retrospective studies linking iron deficiency anaemia to gastrointestinal and some haematological cancers, while large population-based cohorts with clearly defined incident anaemia and longer follow-up are scarce.

WHAT THIS STUDY ADDS

⇒ In this large population-based cohort, we provide 18-month risk estimates for incident cancer and all-cause mortality following incident anaemia, defined by a documented transition from normal haemoglobin to anaemia and compared with non-anaemic sex- and age-matched controls. We show that the routinely measured mean corpuscular volume (MCV) offers clinically useful risk stratification, with microcytosis indicating higher cancer risk, especially digestive and haematological cancers, while macrocytosis is more strongly associated with mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings support structured safety-netting and continued follow-up after incident anaemia, even when initial assessments do not identify cancer, and demonstrate the value of incorporating anaemia patterns and MCV into early risk-stratification tools for cancer detection. They also point to a need for future research on longitudinal haemoglobin trajectories and multi-marker profiles (such as anaemia, MCV combined with thrombocytosis and reticulocytes) to further refine cancer risk stratification.

Conclusions IA is a strong marker of both IC and ACM in routine care. Microcytic anaemia should prompt timely gastrointestinal evaluation, while macrocytic anaemia warrants broader assessments for comorbid conditions and systemic disease. Persistently elevated risks underscore the need for structured safety-netting and

continued follow-up after IA, even without a cancer identification. Our findings highlight the value of using anaemia patterns and MCV in early risk stratification.

INTRODUCTION

Cancer incidence is projected to increase from 18 million in 2020 to 28 million by 2040.¹ Survival remains strongly dependent on stage at diagnosis, underscoring the importance of timely detection.² Most cancers are diagnosed after presentation in primary care, where symptoms are usually benign.³ General practitioners must therefore balance the need for prompt investigation against the risk of over-referral, often with limited clinical information.

Several risk assessment models have been proposed to support early cancer diagnosis, but reliance on coded symptoms limits their utility, and implementation in clinical practice has proved difficult.^{4,5} Objective and feasible biomarkers are needed to improve cancer risk assessment in everyday practice.⁶

Anaemia, particularly iron deficiency anaemia (IDA), is a well-established marker of gastrointestinal malignancies, reflecting possible occult bleeding.^{7,8} It is also a common but non-specific finding in the primary care population, especially in pre-menopausal women and older adults, and among patients who are later diagnosed with non-gastrointestinal cancers.^{9,10} A recent Danish cohort study reported that incident anaemia in primary care was strongly associated with cancer within 12 months. However, anaemia of inflammation, which may contribute to this association, is seldom diagnosed in routine primary care.^{11–13} Mean corpuscular volume (MCV), routinely measured alongside haemoglobin (Hb) in primary care, provides a basic indication of whether anaemia is microcytic, normocytic or macrocytic. These patterns can reflect different underlying mechanisms, but the role of MCV in cancer risk assessment remains unclear.

Existing evidence on the associations between incident anaemia and incident cancer is mainly derived from small or retrospective studies linking IDA to gastrointestinal and some haematological cancers, with several studies being limited to a follow-up of 12 months.^{11,14–16} Large population-based cohorts with clearly defined incident anaemia and longer follow-up examining the association between incident anaemia and cancer in general are thus scarce. The Stockholm Early Detection of Cancer Study (STEADY-CAN)¹⁷ is a large population-based cohort including data on anaemia, routinely collected laboratory data and cancer that can be used to rectify these shortcomings. In primary care, a follow-up period of around 18 months offers a clinically meaningful window for investigating potential associations between incident anaemia and subsequent cancer diagnosis, as symptoms, laboratory abnormalities and the diagnostic work-up often evolve gradually in this setting.

Despite the clinical importance of distinguishing between different causes of anaemia in primary care,

no large population-based studies have evaluated how incident anaemia, or routinely available markers such as MCV, relates to short- to mid-term cancer risk. Generating robust, clinically applicable risk estimates could support earlier and more targeted investigations, reduce diagnostic delays and improve cancer detection in everyday primary care.

Aim

To assess sex- and age-specific associations between incident anaemia and incident cancer within 18 months of the incident anaemia diagnosis, with all-cause mortality (ACM) as a competing risk, using routine practice data from the population-based STEADY-CAN cohort.¹⁷ In addition, we intended to examine how MCV modifies these risks.

METHODS

Data sources and study setting

The STEADY-CAN cohort includes virtually all adults aged ≥ 18 years residing in Stockholm County, Sweden, during 2011–2021, totalling 2 732 005 individuals.¹⁷ Laboratory test results are linked with regional and national administrative health registers, providing comprehensive information on healthcare use, diagnoses and prescribed medications. Full details of the STEADY-CAN cohort are provided in the published cohort profile.¹⁷

Sweden has a tax-funded healthcare system providing universal coverage for all legal residents. Stockholm County, the most populous region in Sweden, has about 2.4 million inhabitants. Hb testing is one of the most frequently performed laboratory investigations in both emergency and routine care, being requested for diverse reasons, including investigations of fatigue, infections, chronic disease monitoring and routine assessments. In the STEADY-CAN cohort, 77% of individuals had at least one Hb measurement, with an average of 5–6 tests per person.¹⁷

Study population

The present STEADY-CAN Anaemia study included individuals in the STEADY-CAN cohort with incident anaemia (cases/exposed) observed between 1 January 2012 and 30 June 2020 who had lived in Stockholm County during the full year before the diagnosis date for incident anaemia (index date), had no previous cancer diagnosis at index date, had at least two Hb assessments on separate dates on or before index date, and had an MCV value measured at the same date as the last Hb measure. Anaemia was defined as Hb < 130 g/L for men and < 120 g/L for women, according to the WHO's criteria.¹⁸ Those with prevalent anaemia as of 31 December 2011, defined as any International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) code D50–D64 or Y44 recorded during 1996–2011, or an Hb value below the sex-specific threshold during 2011, were excluded. Incident anaemia was defined as having an Hb value below

the sex-specific threshold at any time between 1 January 2012 and 30 June 2020, after all previous Hb values had been within the normal range, defined as 130–170 g/L for men and 120–150 g/L for women, according to commonly applied reference intervals.¹⁹ Individuals with Hb >170 g/L for men and >150 g/L for women before the index date were thus excluded. Hb values outside ± 5 SDs from the mean (31.2–229.7 g/L) were excluded to minimise the influence of measurement errors. When multiple Hb values were recorded for the same date, the highest value was used. A previous cancer diagnosis (excluding non-melanoma skin cancer) was defined as having a cancer recorded in the Swedish Cancer Register during the period from 1 January 1992 up to and including the index date.

For each exposed individual, a 1:1 sex- and age-matched unexposed control was selected from participants fulfilling the above-mentioned criteria on the index date of the matched case, except that the controls should have no incident anaemia at this date. Age-matching required the age of the matched control to be within ± 365 days of the case's age. Index dates for controls were set to the index date of the matched case. Cases with no matching controls were excluded. In total, 190 057 cases and 190 057 controls were included in the study (figure 1). Since the design allowed cases to be selected as controls for other cases before themselves becoming cases, and an individual might be a control for several cases, the 380 114 cases and controls consisted of 307 752 unique individuals, with each control on average being matched to 1.6 cases.

Outcome

Participants were followed for 18 months (549 days) from the index date until the date of cancer diagnosis, death from any cause (ACM) or migration from Stockholm County, whichever occurred first. Controls were included in the study and followed from the index date of their matched case. The primary outcome was incident cancer (excluding non-melanoma skin cancer), defined as the date of the first registration in the Swedish Cancer Register during follow-up, with ACM treated as a competing event.

Study variables

Participants were characterised by sex and age at the index date, derived from their Swedish Personal Identification Numbers.²⁰ Due to pseudonymisation of the data, resulting in only the year and month of birth being available, age was calculated by assigning the 15th of the month of birth as the date of birth. For age-stratified analyses, controls were assigned to the age group of their matched case. Comorbidity burden was assessed with the Charlson Comorbidity Index (CCI),²¹ calculated using ICD-10 codes registered during the year before index date, with ICD-10 coding according to Quan *et al.*²² and weights from Charlson *et al.*²¹ excluding the comorbidities 'Any malignancy, including lymphoma and leukaemia,

except malignant neoplasm of skin' and 'Metastatic solid tumour'. Healthcare contact frequency was defined as the number of outpatient healthcare contacts registered during the year before the index date. Laboratory values included in the study consisted of Hb (g/L) and MCV (fL) measured at the index date for cases, while for controls, the values from the last date with available measurements on or before the index date of the matched case were used. MCV was categorised as microcytic (<82 fL), normocytic (82–98 fL) or macrocytic (>98 fL), while anaemia was classified by severity as mild (Hb \geq 110 g/L), moderate (80–109 g/L) or severe (<80 g/L), in accordance with WHO criteria.¹⁸ Incident cancers were categorised into organ-specific groups according to ICD-10 codes.

Statistical analyses

Categorical variables are summarised as frequencies and percentages, n (%), while continuous variables are reported as mean (SD). Time-to-event analyses for exposure status (case/control) with the two possible outcomes incident cancer/ACM were performed using adjusted and unadjusted sex-stratified piecewise competing-risks multi-state Cox regression models, resulting in cause-specific HRs. To account for dependencies introduced by the study design, the regression models were stratified on matched pairs and clustered on observations from the same individual. To allow the association between incident anaemia and incident cancer/ACM to vary over time, we modelled incident anaemia using time-dependent coefficients with cut points at 91, 183 and 366 days, yielding separate estimates for 0–3, 3–6, 6–12 and 12–18 months of follow-up. In sub-analyses, the models were additionally stratified by age group. Adjusted models included age (years), CCI score (points), healthcare contact frequency and MCV class (using normocytic as the reference group) as covariates. Results are presented as cause-specific HRs with 95% CIs. All analyses were performed in R V.4.4.2 or higher (R Foundation for Statistical Computing, Vienna, Austria). Two-sided p values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics and status at follow-up for the 380 114 participants are presented in table 1. Incident anaemia was more common among females than males, with 120 373 (63.6%) of the 190 057 cases included in the study being female, compared with 69 684 (36.7%) male cases. The female cases were considerably younger than the male cases, with a mean (SD) age of 52.5 (21.6) years, compared with 63.6 (17.2) years for the male cases. A majority (n=63 796; 53.0%) of the female cases were <50 years old, compared with only 21.2% (n=14 767) among male cases. The mean (SD) Hb was 122 (9.9) g/L for male cases and 112 (8.6) g/L for female cases, compared with 149 (8.6) g/L for male controls and 135 (6.9) g/L for female controls. Anaemia was predominantly mild (91.5% in males; 77.7% in females), with only 0.9%

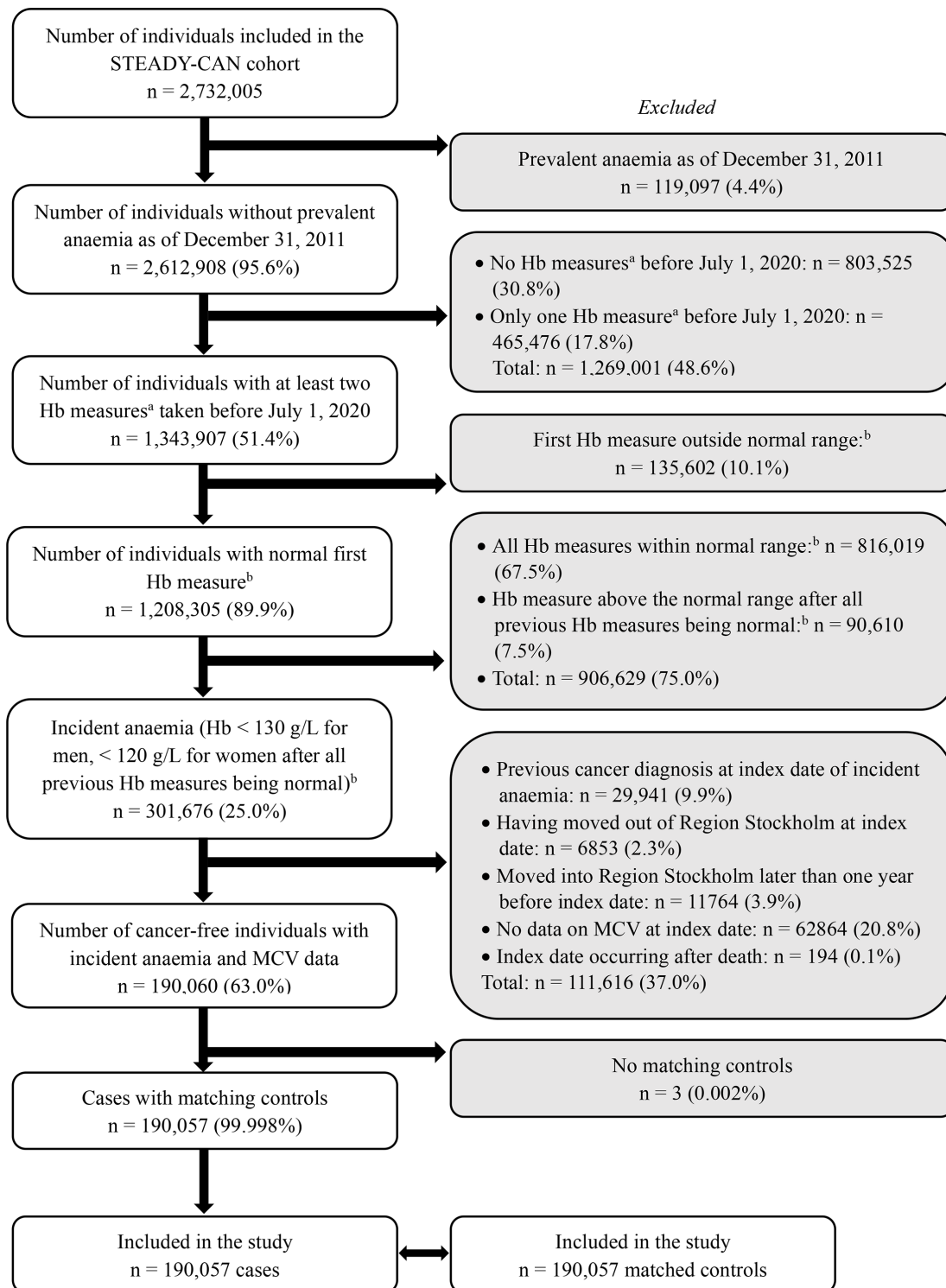


Figure 1 Flowchart of the inclusion process for the Stockholm Early Detection of Cancer Study Anaemia study. ^aExcluding Hb measures outside ± 5 SDs from the mean (31.2–229.7 g/L). ^bNormal Hb range: 130–170 g/L for men and 120–150 g/L for women. Hb, haemoglobin; MCV, mean corpuscular volume.

(n=620) of males and 1.1% (n=1302) of female cases having severe anaemia (<80 g/L).

The comorbidity burden was relatively low, with mean (SD) CCI scores of 0.57 (1.00) points for male cases and 0.46 (0.89) points for male controls, compared with 0.27 (0.68) points for female cases and 0.26 (0.63) points for female controls. Notably, 66.1% (n=46 059) of male cases

and 70.9% (n=49 415) of male controls had no comorbidity according to CCI, with the corresponding values for females being even higher at 81.7% (n=98 306) for female cases and 81.1% (n=97 681) for female controls. The healthcare contact frequency was only marginally higher among cases than controls, with a mean (SD) of 19 (47) encounters during the year before index date for

Table 1 Baseline characteristics and status at follow-up after 18 months for the 380 114 participants in the Stockholm Early Detection of Cancer Study Anaemia study

Variable	Male		Female	
	Cases n=69 684	Controls n=69 684	Cases n=120 373	Controls n=120 373
Age (years), mean (SD)*	63.6 (17.2)	63.5 (17.1)	52.5 (21.6)	52.5 (21.5)
Age group, n (%)†				
<50 years old	14 767 (21.2)	14 767 (21.2)	63 796 (53.0)	63 796 (53.0)
50–59 years old	10 765 (15.4)	10 765 (15.4)	11 589 (9.6)	11 589 (9.6)
60–69 years old	15 304 (22.0)	15 304 (22.0)	12 287 (10.2)	12 287 (10.2)
70–79 years old	17 092 (24.5)	17 092 (24.5)	14 695 (12.2)	14 695 (12.2)
≥80 years old	11 756 (16.9)	11 756 (16.9)	18 006 (15.0)	18 006 (15.0)
B-haemoglobin (g/L), mean (SD)‡	122 (9.9)	149 (8.6)	112 (8.6)	135 (6.9)
Anaemia classification, n (%)‡				
Mild (Hb≥110 g/L)	63 783 (91.5)	N/A	93 535 (77.7)	N/A
Moderate (Hb 80–109 g/L)	5281 (7.6)	N/A	25 536 (21.2)	N/A
Severe (Hb<80 g/L)	620 (0.9)	N/A	1302 (1.1)	N/A
CCI (points), mean (SD)§	0.57 (1.00)	0.46 (0.89)	0.27 (0.68)	0.26 (0.63)
CCI group, n (%)§				
0 points	46 059 (66.1)	49 415 (70.9)	98 306 (81.7)	97 681 (81.1)
1–2 points	19 452 (27.9)	17 432 (25.0)	19 583 (16.3)	20 838 (17.3)
3–4 points	3520 (5.1)	2364 (3.4)	2174 (1.8)	1653 (1.4)
≥5 points	653 (0.9)	473 (0.7)	310 (0.3)	201 (0.2)
HCF, mean (SD)	19 (47)	17 (38)	20 (42)	19 (38)
B-MCV (fL), mean (SD)‡	90.6 (6.7)	91.1 (5.0)	88.9 (6.6)	90.6 (4.8)
B-MCV classification, n (%)‡				
Microcytic (<82 fL)	4336 (6.2)	1382 (2.0)	13 588 (11.3)	2998 (2.5)
Normocytic (82–98 fL)	59 012 (84.7)	63 822 (91.6)	100 405 (83.4)	111 693 (92.8)
Macrocytic (>98 fL)	6336 (9.1)	4480 (6.4)	6380 (5.3)	5682 (4.7)
Status at 18-month follow-up, n (%)				
Censored	60 167 (86.3)	66 250 (95.1)	112 239 (93.2)	116 989 (97.2)
Alive	59 453 (85.3)	65 506 (94.0)	110 195 (91.5)	114 972 (95.5)
Moved out of region Stockholm	714 (1.0)	744 (1.1)	2044 (1.7)	2017 (1.7)
Incident cancer	4331 (6.2)	1675 (2.4)	3363 (2.8)	1361 (1.1)
Dead from any cause (ACM)	5186 (7.4)	1759 (2.5)	4771 (4.0)	2023 (1.7)

Significant p values are given in bold.

*Measured at index date.

†Controls are included in the age groups of their matched cases.

‡Measured at index date for cases and at the latest date of measurement≤index date for controls.

§Calculated using ICD-10 codes registered during the year before index date, with ICD-10 coding according to Quan *et al*²² and weights from Charlson *et al*,²¹ excluding the comorbidities 'Any malignancy, including lymphoma and leukaemia, except malignant neoplasm of skin' and 'Metastatic solid tumour'.

ACM, all-cause mortality; CCI, Charlson Comorbidity Index; Hb, haemoglobin; HCF, healthcare contact frequency; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; MCV, mean corpuscular volume; N/A, not applicable.

male cases and 17 (38) for male controls; among females, the corresponding values were 20 (42) for cases and 19 (38) for controls. Microcytosis was more common in female cases (n=13 588; 11.3%) than male cases (n=4336; 6.2%), while macrocytosis was more common in male cases (n=6336; 9.1%) than female cases (n=6380; 5.3%).

Incident cancer and ACM

For both sexes, the number of incident cancers and deaths was higher among cases than controls (table 1). The ACM rate over the whole follow-up period was 7.4% (n=5186) for male cases, 4.0% (n=4771) for female cases, 2.5% (n=1759) for male controls and 1.7% (n=2023) for

female controls. In comparison, 6.2% (n=4331) of male cases and 2.8% (n=3363) of female cases were diagnosed with incident cancer, with the corresponding values for male and female controls being 2.4% (n=1675) and 1.1% (n=1361), respectively.

Although overall ACM exceeded cancer incidence during follow-up, cancer incidence exceeded ACM among cases aged <50 years (online supplemental figure S1a, b). Among cases aged ≥ 50 years, cancer incidence exceeded ACM during the early months of follow-up, whereas ACM predominated later in follow-up, particularly among the oldest participants. Moreover, the incident cancer rate for the entire follow-up period was higher than the corresponding ACM rate for both sexes across all age groups, except those aged ≥ 80 years, for whom death was more common than incident cancer (online supplemental table S1). Notably, for cases, the incident cancer rate was lower among those aged ≥ 80 years than those aged 70–79 years (online supplemental figure S2). This suggests that the observed higher ACM than incident cancer rate over the whole follow-up period is entirely driven by the high mortality among those aged ≥ 80 years.

Among male cases aged ≥ 50 years, both incident cancer and ACM increased steeply during the first few months of follow-up and continued to rise at a relatively steep rate, with no sign of plateauing, although the increase in cancer incidence started to attenuate after approximately 6 months (online supplemental figure S1a). A similar pattern was observed for ACM among female cases aged ≥ 50 years, whereas the incident cancer curve showed stronger attenuation towards the end of the follow-up period (online supplemental figure S2b). In contrast, curves for unexposed individuals remained low and stable throughout the whole follow-up period. Among individuals aged ≥ 50 years, the incident cancer curves for cases and controls show similar gradients after approximately 6 months, whereas the ACM curves continue to diverge throughout follow-up. This suggests a sustained risk of death due to incident anaemia beyond 18 months, while the risk of incident cancer seems to abate after 12 months.

Risk estimates

Results from sex-stratified piecewise competing risks Cox regression analyses for the outcomes incident cancer/ACM after 18 months of follow-up are given in table 2. In adjusted analyses, incident anaemia was associated with significantly increased risks of incident cancer during 0–3, 3–6 and 6–12 months after index date (all $p < 0.001$). The magnitude of this association decreased over time and was non-significant for both sexes at 12–18 months of follow-up. During the first 3 months of follow-up, incident anaemia implied a 9.17-fold higher risk of incident cancer in males and an 8.25-fold higher risk in females. These risks decreased to 2.18 for males and 1.84 for females during the period 3–6 months after index date and to 1.32 for males and 1.31 for females during the period 6–12 months after index date.

Incident anaemia was associated with significantly increased risks of death for both sexes throughout the whole follow-up period (all $p < 0.001$). During the first 3 months, incident anaemia implied an 8.50-fold higher risk of death in males and a 6.14-fold higher risk in females, decreasing to 3.35 and 2.59, 2.26 and 1.90, and 2.03 and 1.77 during 3–6, 6–12 and 12–18 months of follow-up, respectively. Individuals with severe anaemia exhibited a higher incident cancer rate than those with mild or moderate anaemia. However, for ACM, this was less pronounced among females and not observed among males (figure 2a). In age-stratified adjusted models (online supplemental figure S3a–d), for both sexes, incident anaemia during the 0–3 and 3–6 months of follow-up periods was associated with significantly increased risks of both incident cancer and death in all age groups. Notably, among males, incident anaemia implied a 63.1-fold higher risk of incident cancer during 0–3 months of follow-up in those aged <50 years and a 28.1-fold higher risk of death in those aged 50–59 years (online supplemental figure S3a). For the 6–12 months of follow-up period, the association between incident anaemia and increased risk of incident cancer remained significant for all except those aged <50 years and males aged ≥ 80 years, while the association with increased risk of death was significant for all groups except females aged <50 years (online supplemental figure S3c). Finally, during the 12–18 months of follow-up period, the association between incident anaemia and increased risk of incident cancer was significant only for males aged <50 years and females aged 50–59 or 70–79 years, while significant associations between incident anaemia and increased risk of death were observed for all groups except females aged <50 years (online supplemental figure S3d).

Microcytosis was also associated with significantly higher risks of incident cancer in the adjusted analyses, where microcytic males were 1.83 times more likely than those with normocytosis to experience incident cancer during the 18-month follow-up period ($p < 0.001$), with the corresponding value for females being 1.33 ($p < 0.001$). Although macrocytosis was not significantly associated with incident cancer among either sex in the adjusted analyses, it was significantly associated with ACM, with macrocytosis in males implying a 1.35 times higher risk of ACM compared with those with normocytosis ($p < 0.001$), and macrocytosis in women implying a 1.43 times higher risk of ACM compared with those with normocytosis ($p < 0.001$). However, no significant association was found between microcytosis and ACM in the adjusted analyses.

For both sexes, the ACM rate increased steeply among cases with macrocytosis during the whole follow-up period (figure 2b). However, the ACM rate for other MCV classes and the incident cancer rate for all MCV classes showed a considerably slower increase among females.

Higher comorbidity, as measured by CCI, had no significant effects on incident cancer in the adjusted analyses. A higher CCI was, however, significantly associated with increased ACM among both sexes, with the

Table 2 Results from sex-stratified piecewise competing risks multi-state Cox regression analyses for the outcomes incident cancer and death from any cause (ACM) after 18-month follow-up for the 380 114 participants in the Stockholm Early Detection of Cancer Study Anaemia study, using time dependent coefficients for incident anaemia in the form of a step function with cut points at 3-, 6- and 12-month follow-up

Sex	Outcome	Interval		Unadjusted		Adjusted*	
		(months)	Variable	HR (95% CI)	P value	HR (95% CI)	P value
Male	Cancer	0–3	Incident anaemia	9.72 (8.61 to 10.98)	<0.001	9.17 (8.12 to 10.36)	<0.001
		3–6	Incident anaemia	2.24 (1.99 to 2.53)	<0.001	2.18 (1.94 to 2.46)	<0.001
		6–12	Incident anaemia	1.35 (1.24 to 1.48)	<0.001	1.32 (1.20 to 1.44)	<0.001
		12–18	Incident anaemia	1.10 (1.00 to 1.21)	0.038	1.08 (0.98 to 1.18)	0.104
		0–18	CCI (points)†	0.99 (0.96 to 1.02)	0.514	1.00 (0.95 to 1.05)	0.963
		0–18	HCF	0.999 (0.997 to 1.000)	<0.001	0.999 (0.997 to 1.000)	0.004
		0–18	B-MCV classification				
			Normocytic (82–98 fL)	Ref.		Ref.	
			Microcytic (<82 fL)	4.88 (4.05 to 5.89)	<0.001	1.83 (1.51 to 2.21)	<0.001
		Macrocytic (>98 fL)	1.34 (1.22 to 1.48)	<0.001	1.07 (0.94 to 1.22)	0.279	
	Death	0–3	Incident anaemia	8.29 (7.33 to 9.38)	<0.001	8.50 (7.48 to 9.65)	<0.001
		3–6	Incident anaemia	3.36 (2.96 to 3.81)	<0.001	3.35 (2.96 to 3.80)	<0.001
		6–12	Incident anaemia	2.27 (2.08 to 2.47)	<0.001	2.26 (2.07 to 2.47)	<0.001
		12–18	Incident anaemia	2.08 (1.91 to 2.27)	<0.001	2.03 (1.85 to 2.23)	<0.001
		0–18	CCI (points)†	1.36 (1.32 to 1.41)	<0.001	1.36 (1.30 to 1.41)	<0.001
		0–18	HCF	1.004 (1.003 to 1.005)	<0.001	1.002 (1.001 to 1.003)	<0.001
		0–18	B-MCV classification				
			Normocytic (82–98 fL)	Ref.		Ref.	
		Microcytic (<82 fL)	1.84 (1.52 to 2.23)	<0.001	1.04 (0.78 to 1.39)	0.791	
	Macrocytic (>98 fL)	1.56 (1.44 to 1.69)	<0.001	1.35 (1.20 to 1.51)	<0.001		
Female	Cancer	0–3	Incident anaemia	8.60 (7.58 to 9.76)	<0.001	8.25 (7.25 to 9.38)	<0.001
		3–6	Incident anaemia	1.90 (1.68 to 2.16)	<0.001	1.84 (1.62 to 2.10)	<0.001
		6–12	Incident anaemia	1.34 (1.21 to 1.47)	<0.001	1.31 (1.19 to 1.45)	<0.001
		12–18	Incident anaemia	1.05 (0.95 to 1.17)	0.297	1.04 (0.93 to 1.15)	0.500
		0–18	CCI (points)†	0.97 (0.93 to 1.01)	0.139	1.02 (0.96 to 1.07)	0.539
		0–18	HCF	0.998 (0.997 to 1.000)	<0.001	0.999 (0.997 to 1.000)	0.014
		0–18	B-MCV classification				
			Normocytic (82–98 fL)	Ref.		Ref.	
			Microcytic (<82 fL)	3.49 (3.00 to 4.06)	<0.001	1.33 (1.11 to 1.59)	0.001
		Macrocytic (>98 fL)	1.24 (1.10 to 1.40)	<0.001	1.09 (0.93 to 1.26)	0.263	
	Death	0–3	Incident anaemia	5.97 (5.33 to 6.69)	<0.001	6.14 (5.48 to 6.88)	<0.001
		3–6	Incident anaemia	2.59 (2.32 to 2.90)	<0.001	2.59 (2.30 to 2.92)	<0.001
		6–12	Incident anaemia	1.90 (1.75 to 2.05)	<0.001	1.90 (1.75 to 2.07)	<0.001
		12–18	Incident anaemia	1.83 (1.68 to 1.99)	<0.001	1.77 (1.62 to 1.94)	<0.001
		0–18	CCI (points)†	1.43 (1.38 to 1.49)	<0.001	1.46 (1.40 to 1.53)	<0.001
		0–18	HCF	1.002 (1.001 to 1.003)	<0.001	1.001 (1.000 to 1.002)	<0.001
		0–18	B-MCV classification				
			Normocytic (82–98 fL)	Ref.		Ref.	
		Microcytic (<82 fL)	1.99 (1.71 to 2.31)	<0.001	0.98 (0.81 to 1.17)	0.786	
	Macrocytic (>98 fL)	1.61 (1.48 to 1.76)	<0.001	1.43 (1.28 to 1.61)	<0.001		

Significant p values are given in bold.

*Adjusted for all variables included in the table and additionally for age (years) as a continuous variable.

†Calculated using ICD-10 codes registered during the year before index date, with ICD-10 coding according to Quan *et al*²² and weights from Charlson *et al*,²¹ excluding the comorbidities ‘Any malignancy, including lymphoma and leukaemia, except malignant neoplasm of skin’ and ‘Metastatic solid tumour’.

ACM, all-cause mortality; CCI, Charlson Comorbidity Index; HCF, healthcare contact frequency; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; MCV, mean corpuscular volume; Ref., reference group.

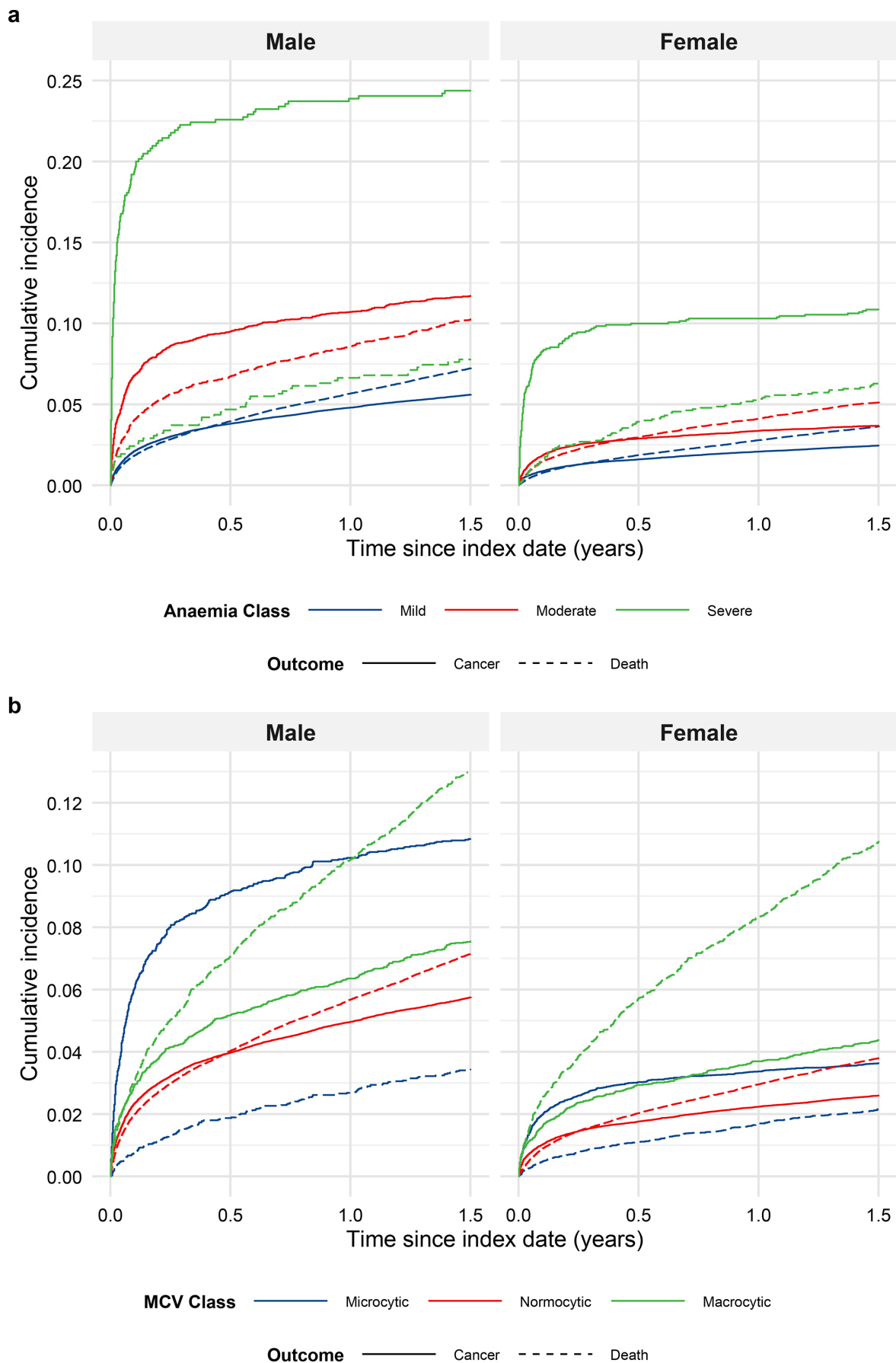


Figure 2 Sex-stratified cumulative incidence of cancer and death from any cause among cases during 18 months of follow-up from the index date according to (a) anaemia and (b) mean corpuscular volume (MCV) class.

risk being 1.36 times higher per additional CCI point among males ($p<0.001$) and 1.46 times higher among females ($p<0.001$). Higher healthcare contact frequency implied lower risks of incident cancer among both men (HR 0.999; $p=0.004$) and women (HR 0.999; $p=0.014$), but higher risks of death (HR 1.002 for men, HR 1.001 for women; both $p<0.001$).

Cancer types

Organ-specific cases of incident cancer are given in table 3. Notably, *malignant neoplasms of digestive organs* (ICD-10 code C15–C26) were the most common incident cancer among both male ($n=1475$; 34.1%) and female ($n=1181$; 35.1%) cases, with *colorectal cancer* (CRC; C18–C20) constituting 17.8% ($n=770$) and 22.9% ($n=711$) of

Table 3 Organ-specific cases of incident cancer according to ICD-10 codes among participants with incident cancer in the Stockholm Early Detection of Cancer Study Anaemia study during the 18-month follow-up period, n (%)

Type of cancer	ICD-10 code	Male		Female	
		Cases n=4331 (6.2%)	Controls n=1675 (2.4%)	Cases n=3363 (2.8%)	Controls n=1361 (1.1%)
Malignant neoplasms of lip, oral cavity and pharynx	C00–C14	47 (1.1)	40 (2.4)	36 (1.1)	24 (1.8)
Malignant neoplasms of digestive organs	C15–C26	1475 (34.1)	300 (17.9)	1181 (35.1)	240 (17.6)
Malignant neoplasm of oesophagus*	C15	78 (1.8)	20 (1.2)	17 (0.5)	7 (0.5)
Malignant neoplasm of stomach*	C16	146 (3.4)	33 (2.0)	69 (2.1)	14 (1.0)
Colorectal cancer	C18–C20	770 (17.8)	146 (8.7)	771 (22.9)	125 (9.2)
Malignant neoplasm of liver and intrahepatic bile ducts*	C22	155 (3.6)	29 (1.7)	34 (1.0)	5 (0.4)
Malignant neoplasm of pancreas*	C25	206 (4.8)	54 (3.2)	161 (4.8)	63 (4.6)
Malignant neoplasms of respiratory and intrathoracic organs	C30–C39	386 (8.9)	143 (8.5)	285 (8.5)	107 (7.9)
Malignant neoplasm of bronchus and lung*	C34	342 (7.9)	128 (7.6)	262 (7.8)	99 (7.3)
Malignant neoplasms of bone and articular cartilage	C40–C41	3 (0.1)	1 (0.1)	4 (0.1)	2 (0.1)
Malignant melanoma of skin*	C43	77 (1.8)	94 (5.6)	70 (2.1)	96 (7.1)
Malignant neoplasms of mesothelial and soft tissue	C45–C49	22 (0.5)	9 (0.5)	32 (1.0)	3 (0.2)
Malignant neoplasm of breast*	C50	5 (0.1)	3 (0.2)	343 (10.2)	375 (27.6)
Malignant neoplasms of female genital organs	C51–C58	N/A	N/A	345 (10.3)	150 (11.0)
Gynaecological cancer	C51–C54, C559, C569, C570	N/A	N/A	330 (9.8)	149 (10.9)
Malignant neoplasms of male genital organs	C60–C63	925 (21.4)	650 (38.8)	N/A	N/A
Malignant neoplasm of prostate*	C61	888 (20.5)	637 (38.0)	N/A	N/A
Malignant neoplasms of urinary tract	C64–C68	391 (9.0)	189 (11.3)	177 (5.3)	71 (5.2)
Malignant neoplasms of eye, brain and other parts of central nervous system	C69–C72	44 (1.0)	33 (2.0)	46 (1.4)	42 (3.1)
Malignant neoplasms of thyroid and other endocrine glands	C73–C75	70 (1.6)	25 (1.5)	96 (2.9)	83 (6.1)
Malignant neoplasms of ill-defined, secondary and unspecified sites	C76–C80	87 (2.0)	20 (1.2)	184 (5.5)	47 (3.5)
Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue	C81–C96	691 (16.0)	138 (8.2)	504 (15.0)	105 (7.7)
Non-Hodgkin's lymphoma*	C82–C85	246 (5.7)	67 (4.0)	174 (5.2)	52 (3.8)
Leukaemia*	C91–C95	208 (4.8)	42 (2.5)	150 (4.5)	24 (1.8)
Myelodysplastic syndromes and other neoplasms of uncertain or unknown behaviour of lymphoid, haematopoietic and related tissue	D46–D47	118 (2.7)	31 (1.9)	62 (1.8)	17 (1.2)

Includes only individuals without any previous cancer registered in the Swedish Cancer Register during the period from 1 January 1992 to the date of diagnosis of the specified cancer. No one had the diagnoses 'Malignant neoplasms of independent (primary) multiple sites' (ICD-10 code C97) or 'Polycythaemia vera' (ICD-10 code D45). The most common cancer type is given in bold.

*Included in the GLOBOCAN 2020 list with $\geq 1.0\%$ of all new cancer cases worldwide during 2020.

ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; N/A, not applicable.

the total number of observed incident cancers among male and female cases, respectively. CRC was also the most common subgroup among female cases, while prostate cancer was the most common subgroup among male cases at 20.5% (n=888). Another large cancer group among cases was *malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue* (C81–C96) at 16.0% (n=691) for male cases and 15.0% (n=504) for female cases.

Among male controls, the most common cancers were *malignant neoplasms of male genital organs* (C60–C63) at 38.8% (n=650), which almost entirely consisted of prostate cancer (38.0%; n=637), and malignant neoplasms of digestive organs at 17.9% (n=300). For female controls, breast cancer was the most common cancer type at 27.6% (n=375), followed by malignant neoplasms of digestive organs at 17.6% (n=240).

DISCUSSION

Incident anaemia was strongly associated with increased risks of incident cancer and ACM across all age groups and in both sexes during the first 12 months after the incident anaemia diagnosis. While microcytosis was linked with elevated incident cancer risks, particularly for CRC, macrocytosis signalled higher ACM without a corresponding increase in incident cancer. This divergent pattern suggests that different mechanisms drive cancer risk and mortality following incident anaemia, with macrocytosis more likely reflecting other systemic diseases than occult malignancy.

Results in context

Previous studies have mainly focused on IDA and its association with gastrointestinal malignancies, particularly CRC, while some studies have also reported associations with haematological cancers.^{11 14 16 23} Our findings are consistent with this literature, demonstrating the highest incident cancer risks for CRC and a substantial proportion of haematological cancers among patients with incident anaemia.

Prior evidence on MCV as a risk indicator of cancer is more limited. Microcytosis has been associated with an increased short-term cancer risk in a large primary care cohort, including colorectal and several other tumour types.²⁴ In clinical practice, microcytic anaemia most commonly reflects IDA. The strong association between microcytosis and digestive cancers observed in the present study is therefore likely driven primarily by iron deficiency and occult gastrointestinal blood loss, consistent with established pathways linking IDA to luminal gastrointestinal malignancy. By contrast, studies of macrocytosis have largely examined underlying causes and prognosis. Macrocytic anaemia in general practice is often related to nutritional deficiency, alcohol use, liver disease or bone marrow disorders and is linked to poorer long-term survival.²⁵ Increased ACM among individuals with elevated MCV has also been reported in population-based

health check-up cohorts and hospital-treated patient groups.^{26 27} In a Swedish population-based study, macrocytic anaemia was rare but carried the highest all-cause and cancer-related mortality.²⁸ These findings align with our observation that macrocytosis within incident anaemia was associated with ACM rather than incident cancer, supporting its interpretation as a marker of broader comorbidity rather than undiagnosed malignancy. This mortality signal is plausibly explained by non-malignant pathways commonly associated with macrocytosis in primary care, including alcohol-associated disease, liver disease, haemolysis and bone marrow disorders such as myelodysplastic syndromes. Alcohol-associated diseases may represent an important contributor to sustained excess mortality, although alcohol exposure could not be directly assessed in this register-based study.

To our knowledge, no previous study has evaluated MCV within incident anaemia, defined by a documented decline from normal Hb levels, in relation to both incident cancer and ACM over the same follow-up period. Recent research on Danish primary care data has shown that new-onset anaemia of inflammation is strongly associated with cancer, with a 12-month cumulative incidence of about 21% among patients without known comorbidities.¹⁴ Our findings confirm prior evidence and show that excess cancer incidence is concentrated within the first year of follow-up.^{11 14–16} This is consistent with anaemia as an early marker of occult malignancy rather than a causal factor. Excess mortality persisted beyond the first year. Future work should evaluate how anaemia interacts with other haematological risk markers (eg, thrombocytosis, leucocytosis or leucopenia)^{29 30} and with Hb dynamics (levels and rates of decline), and test multi-marker decision-support tools to refine risk stratification and inform earlier and more targeted investigation in primary care.

Strengths and limitations

The principal strengths of this study are its scale and coverage. The STEADY-CAN cohort includes virtually all adults in a single healthcare region over a decade, with linked laboratory and administrative records, enabling near-complete follow-up and reducing selection and information bias. A further strength is the internal-comparator design: patients with incident anaemia were compared with anaemia-free individuals within the same cohort. This approach mirrors real-world decision-making in primary care. We also required a documented transition from normal Hb to anaemia, rather than relying solely on a *look-back* window, thereby reducing the risk that chronic cases were misclassified as incident anaemia. Excluding individuals who did not reside in the study region during the year before the index date reduced misclassification and ensured a complete baseline history. The use of piecewise competing-risks Cox regression models allowed for estimation of time-varying coefficients, providing clinically interpretable cause-specific HRs for incident cancer and ACM. An alternative approach would have

been to use subdistribution HRs obtained from Fine-Gray models. However, given our focus on the instantaneous risk among event-free individuals, and in line with recent methodological guidance, we considered cause-specific modelling the most appropriate approach.³¹ Cancer subtypes were analysed descriptively only.

The main limitation is the observational design; results are associative rather than causal. Although we matched on age and adjusted for comorbidity and MCV, residual confounding and selection bias cannot be excluded. Requiring at least two Hb tests reflects routine practice but may have preferentially included individuals undergoing repeat testing, potentially affecting generalisability. The absence of data on consultation reasons introduces potential confounding by indication, since patients tested for Hb may be sicker than the average patient. However, the internal comparator mitigates this by restricting comparisons to the same cohort. Detection bias is possible, but investigation-driven detection would be expected to cluster early diagnoses rather than drive the elevated cancer risk observed across the first year.

We chose an 18-month follow-up period to balance clinical relevance in primary care with the risk of diluting the temporal association between anaemia and subsequently detected cancers. In primary care, diagnostic work-up after new-onset anaemia is often stepwise and may involve initial investigations, referrals and planned re-assessments over several months; an 18-month window therefore captures both the initial diagnostic pathway and intended safety-netting, while acknowledging that excess cancer diagnoses were largely concentrated within the first year. Extending follow-up substantially beyond this window may capture cancers less plausibly related to incident anaemia and increase unrelated background incidence, thereby weakening specificity. Nevertheless, while the excess cancer incidence attenuated after the first year, longer follow-up could provide insight into whether incident anaemia is associated with broader long-term health vulnerability beyond the initial high-risk period.

CCI, which we used for comorbidity adjustment, does not fully capture several common causes of anaemia in primary care, including alcohol use, malnutrition, chronic liver disease, inflammatory conditions and gynaecological blood loss. Laboratory markers that could partly address these mechanisms (eg, liver function tests or inflammatory markers) were not incorporated, as such tests are performed selectively in routine care and were missing for a large proportion of participants. Restricting analyses to individuals with available measurements could have introduced selection bias. To partly address differences in underlying morbidity and healthcare utilisation not captured by CCI, we additionally adjusted for healthcare contact frequency, which complements diagnostic comorbidity measures by reflecting overall healthcare use. Healthcare contact frequency was similar between cases and controls at baseline, supporting comparability between groups in terms of healthcare utilisation. Residual confounding is thus possible, particularly for the

association between macrocytosis and ACM, which is likely to reflect broader comorbidity rather than malignancy.

A further limitation is that MCV was assessed at a single time point at the index date. MCV may fluctuate over time, and a single measurement may therefore misclassify some individuals. We used MCV primarily as a pragmatic marker for broad morphological classification rather than as a precise diagnostic indicator. Repeated MCV measurements were available only for a subset of participants and inclusion of these would likely introduce selection bias related to healthcare utilisation. Any non-differential misclassification of MCV would likely bias associations towards the null.

The applicability of our results may vary across healthcare systems. Screening practices, laboratory testing thresholds and access to diagnostic pathways differ internationally, influencing both the detection of anaemia and the subsequent cancer work-up. Absolute risks may thus differ across settings. However, the relative risk patterns observed, particularly the differential associations by anaemia severity and MCV class, are likely transferable to comparable healthcare systems where anaemia is identified in routine care.

Clinical implications

Incident anaemia is common and may be a relevant risk marker in primary care. A pragmatic way to integrate our findings into decision-making is to use two routinely available parameters, Hb severity and MCV, as an initial risk-stratification trigger to guide initial investigation, referral and follow-up. In men and postmenopausal women, these indices may support pragmatic first-line stratification, and microcytosis should prompt expedited gastrointestinal investigation after confirmation of underlying iron deficiency, particularly in non-menstruating adults, including faecal immunochemical testing (FIT) or referral for gastrointestinal endoscopy, given that digestive cancers accounted for one-third of cases and CRC for nearly one-quarter. In premenopausal women, where menstrual blood loss is common and cancer risk was lower in those aged <50 years, initial management should prioritise gynaecological assessment and iron deficiency confirmation, with gastrointestinal investigation reserved for alarm features, positive FIT or failure to respond to iron supplementation. By contrast, macrocytosis was associated with ACM rather than incident cancer, supporting the need for a broader comorbidity assessment (including alcohol-related and liver disease, and bone marrow disorders) rather than a fast-track cancer referral. Mild anaemia is common but not benign: it carries clear excess risks, particularly in younger males (<50 years old), where the relative risk is largest. With 15%–16% of incident cancers being haematological, the breadth of the spectrum warrants a low threshold for broader haematological work-up beyond Hb and MCV, at minimum a full blood count including reticulocytes

with a differential count and iron studies, especially when systemic red flags (fever, night sweats, weight loss, lymphadenopathy, hepatosplenomegaly) or additional blood count abnormalities (leucocytosis, thrombocytosis, cytopenias) are present. Although our analyses were restricted to Hb and MCV, the observed proportion of haematological cancers is consistent with current recommendations to consider comprehensive haematological evaluation in such cases.

Excess risks emerged early, with increased incident cancer risks concentrated in the first 12 months of follow-up, whereas excess ACM persisted throughout the 18-month follow-up period. A longer follow-up might provide additional insights into longer-term health vulnerability, but this was outside the scope of the present study. These findings support structured follow-ups and repeated risk assessments after the initial diagnostic work-up, rather than a rule-out approach. In practice, this could be operationalised as explicit safety-netting with a documented follow-up plan, including repeat blood counts and clear thresholds for re-assessment or referral if symptoms persist or Hb fails to normalise. From a guideline perspective, men with incident anaemia and several high-risk subgroups (notably those with microcytosis or more severe anaemia) exceed the 3% risk threshold used in the British National Institute for Health and Care Excellence guidance for 2-week-wait referral, supporting rapid investigation at low thresholds in primary care.³² Any future decision-support tools based on anaemia morphology and severity should, however, be implemented cautiously and validated prospectively, as observational risk estimates may be influenced by residual confounding and surveillance bias.

CONCLUSIONS

New-onset anaemia is a strong and sustained risk marker for both incident cancer and all-cause mortality in primary care. Simple morphology offers practical guidance: microcytosis should prompt expedited gastrointestinal investigation, whereas macrocytosis points to broader assessment of comorbidity rather than non-specific fast-track cancer referrals.

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(supporting); methodology (equal); supervision (equal); visualisation (supporting); writing – original draft (supporting); writing – review and editing (equal). PL: conceptualisation (supporting); formal analysis (supporting); funding acquisition (supporting); methodology (equal); supervision (equal); visualisation (supporting); writing – original draft (supporting); writing – review and editing (equal). AR: conceptualisation (supporting); data curation (lead); formal analysis (lead); funding acquisition (supporting); methodology (equal); software (lead); supervision (lead); visualisation (lead); writing – original draft (equal); writing – review and editing (equal) and guarantor. AC: conceptualisation (supporting); formal analysis (supporting); funding acquisition (supporting); methodology (equal); supervision (lead); visualisation (supporting); writing – original draft (supporting); writing – review and editing (equal).

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Ethics approval This study was performed according to the principles of the Declaration of Helsinki. Approval was obtained by the Swedish Ethical Review Authority (Dnr. 2021-05069, 2023-00704-02 and 2025-02072-02). Informed consent for individual participation was waived due to the nature of this register-based study, which used pseudonymised data from national and regional healthcare registers and all data handling complies with national ethical and data protection regulations.

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Data availability statement Data may be obtained from a third party and are not publicly available. The data used in this study consist of pseudonymised individual-level information obtained from Swedish national and regional health data sources, including the Centre for Health Data in Region Stockholm, the National Board of Health and Welfare, and three major laboratory providers: Karolinska Universitetslaboratoriet, SYNLAB Medilab and Unilabs. Due to legal and ethical restrictions under Swedish law, we are not permitted to share the raw data. Access to these data requires ethical approval and agreements with the respective data holders. Interested researchers should contact these organisations directly for information on data access procedures.

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Supplementary data to Incident anaemia as a marker of cancer and all-cause mortality

Supplementary data to
Incident anaemia as a marker of cancer and all-cause mortality: Evidence from 380,114
adults in the population-based Stockholm Early Detection of Cancer Study (STEADY-
CAN) cohort

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Table S1. Status at follow-up after 18 months for the 380,114 participants in the STEADY-CAN Anaemia study according to age, sex, and exposure status

Age (years)	Variable	Male		Female	
		Cases, n (%)	Controls, n (%)	Cases, n (%)	Controls, n (%)
< 50	Censored	14303 (96.9)	14710 (99.6)	63332 (99.3)	63543 (99.6)
	- Alive	14002 (94.8)	14430 (97.7)	61664 (96.7)	61946 (97.1)
	- Moved out of Region Stockholm	301 (2.0)	280 (1.9)	1668 (2.6)	1597 (2.5)
	Incident cancer	249 (1.7)	23 (0.2)	380 (0.6)	215 (0.3)
	Dead from any cause	215 (1.5)	34 (0.2)	84 (0.1)	38 (0.1)
	Total	14767 (100.0)	14767 (100.0)	63796 (100.0)	63796 (100.0)
50–59	Censored	10007 (93.0)	10619 (98.6)	11104 (95.8)	11455 (98.8)
	- Alive	9892 (91.9)	10517 (97.7)	10999 (94.9)	11341 (97.9)
	- Moved out of Region Stockholm	115 (1.1)	102 (0.9)	105 (0.9)	114 (1.0)
	Incident cancer	436 (4.1)	112 (1.0)	374 (3.29)	115 (1.0)
	Dead from any cause	322 (3.0)	34 (0.3)	111 (1.0)	19 (0.2)
	Total	10765 (100.0)	10765 (100.0)	11589 (100.0)	11589 (100.0)
60–69	Censored	13423 (87.7)	14750 (96.4)	11294 (91.9)	12016 (97.8)
	- Alive	13254 (86.6)	14561 (95.1)	11182 (91.0)	11895 (96.8)
	- Moved out of Region Stockholm	169 (1.1)	189 (1.2)	112 (0.9)	121 (1.0)
	Incident cancer	1166 (7.6)	424 (2.8)	668 (5.4)	219 (1.8)
	Dead from any cause	715 (4.7)	130 (0.8)	325 (2.6)	52 (0.4)
	Total	15304 (100.0)	15304 (100.0)	12287 (100.0)	12287 (100.0)
70–79	Censored	14049 (82.2)	16091 (94.1)	12890 (87.7)	14139 (96.2)
	- Alive	13961 (81.7)	15970 (93.4)	12823 (87.3)	14036 (95.5)
	- Moved out of Region Stockholm	88 (0.5)	121 (0.7)	67 (0.5)	103 (0.7)
	Incident cancer	1610 (9.4)	658 (3.8)	1005 (6.8)	366 (2.5)
	Dead from any cause	1433 (8.4)	343 (2.0)	800 (5.4)	190 (1.3)
	Total	17092 (100.0)	17092 (100.0)	14695 (100.0)	14695 (100.0)
≥ 80	Censored	8385 (71.3)	10080 (85.7)	13619 (75.6)	15836 (87.9)
	- Alive	8344 (71.0)	10028 (85.3)	13527 (75.1)	15754 (87.5)
	- Moved out of Region Stockholm	41 (0.3)	52 (0.4)	92 (0.5)	82 (0.5)
	Incident cancer	870 (7.4)	458 (3.9)	936 (5.2)	446 (2.5)
	Dead from any cause	2501 (21.3)	1218 (10.4)	3451 (19.2)	1724 (9.6)
	Total	11756 (100.0)	11756 (100.0)	18006 (100.0)	18006 (100.0)

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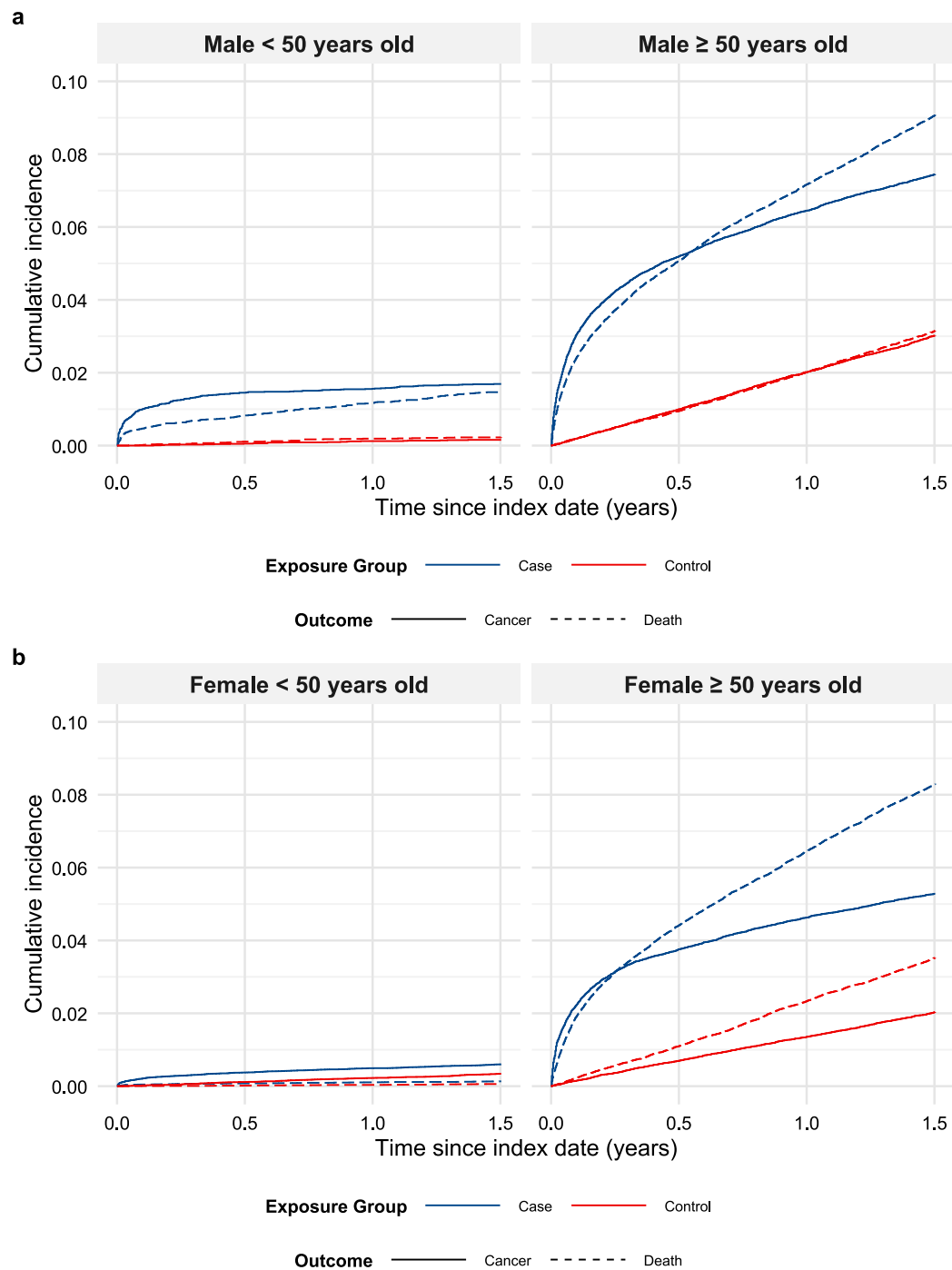


Figure S1. Cumulative incidence of cancer and death from any cause during 18 months of follow-up from index date according to age and exposure status **a.** among males and **b.** among females

Supplementary data to Incident anaemia as a marker of cancer and all-cause mortality

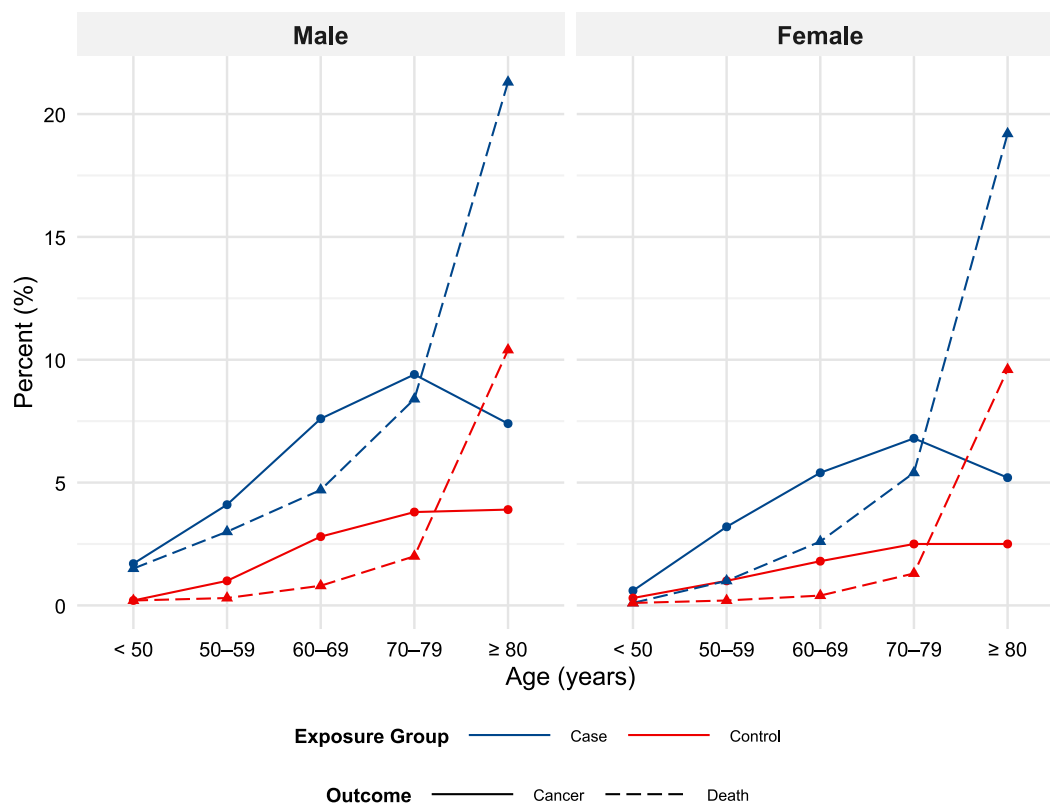


Figure S2. Plot of status at follow-up after 18 months for the 380,114 participants in the STEADY-CAN Anaemia study according to age, sex, and exposure status

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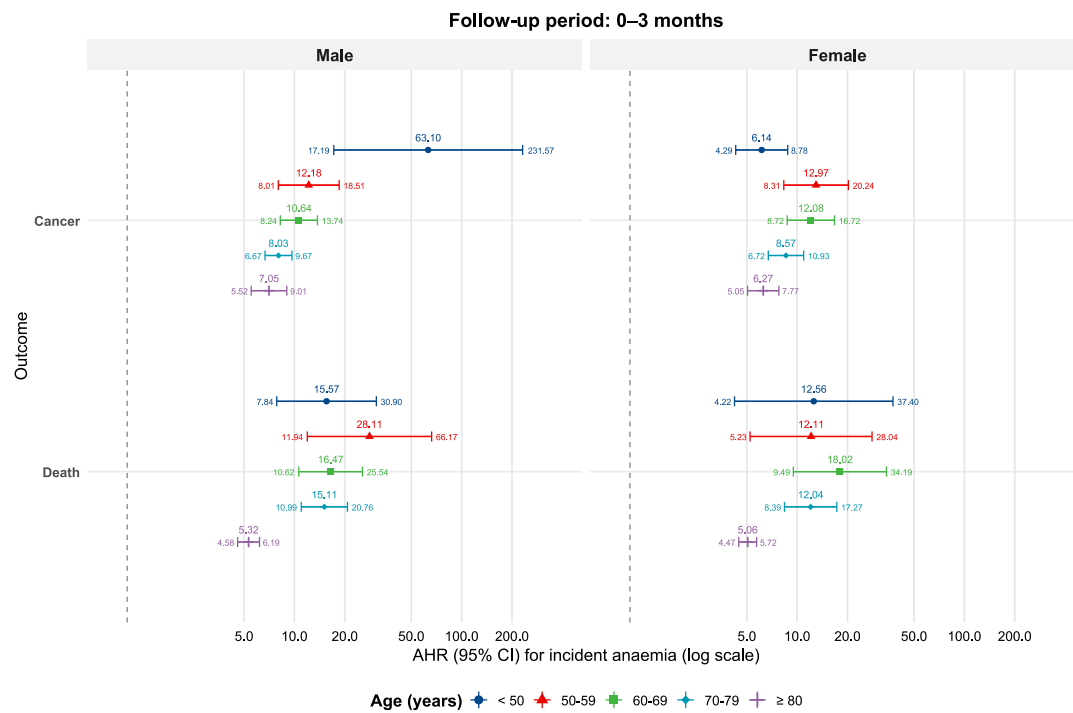


Figure S3a. Adjusted hazard ratios (AHRs) with 95% confidence intervals (CIs) for incident anaemia (log scale) according to sex and age group at 0–3 months follow-up. The results are adjusted for Charlson comorbidity index (CCI) value (points), healthcare contact frequency (HCF), mean corpuscular volume (MCV) class, and age (years).

Supplementary data to Incident anaemia as a marker of cancer and all-cause mortality

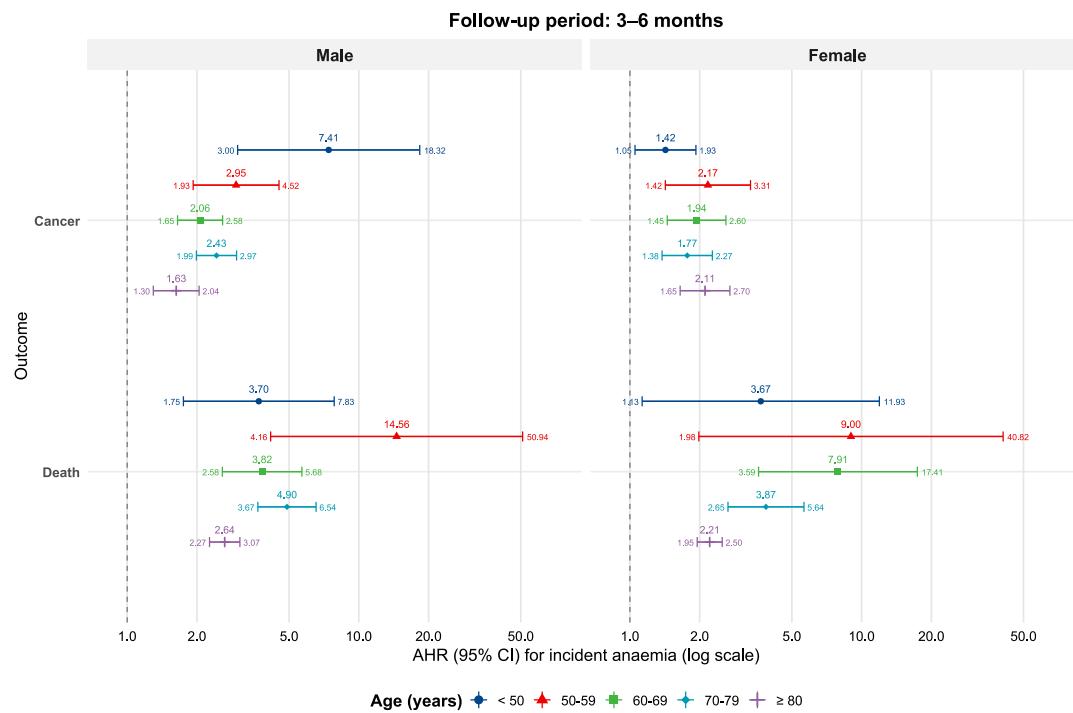


Figure S3b. Adjusted hazard ratios (AHRs) with 95% confidence intervals (CIs) for incident anaemia (log scale) according to sex and age group at 3–6 months follow-up. The results are adjusted for Charlson comorbidity index (CCI) value (points), healthcare contact frequency (HCF), mean corpuscular volume (MCV) class, and age (years).

Supplementary data to Incident anaemia as a marker of cancer and all-cause mortality

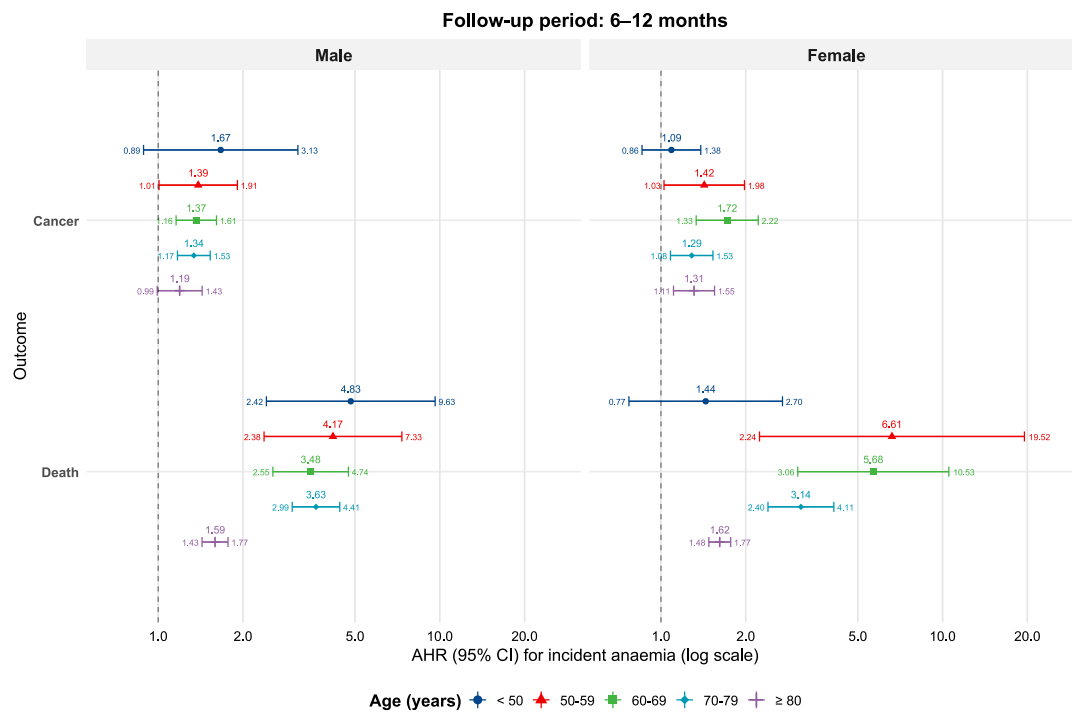


Figure S3c. Adjusted hazard ratios (AHRs) with 95% confidence intervals (CIs) for incident anaemia (log scale) according to sex and age group at 6–12 months follow-up. The results are adjusted for Charlson comorbidity index (CCI) value (points), healthcare contact frequency (HCF), mean corpuscular volume (MCV) class, and age (years).

Supplementary data to Incident anaemia as a marker of cancer and all-cause mortality

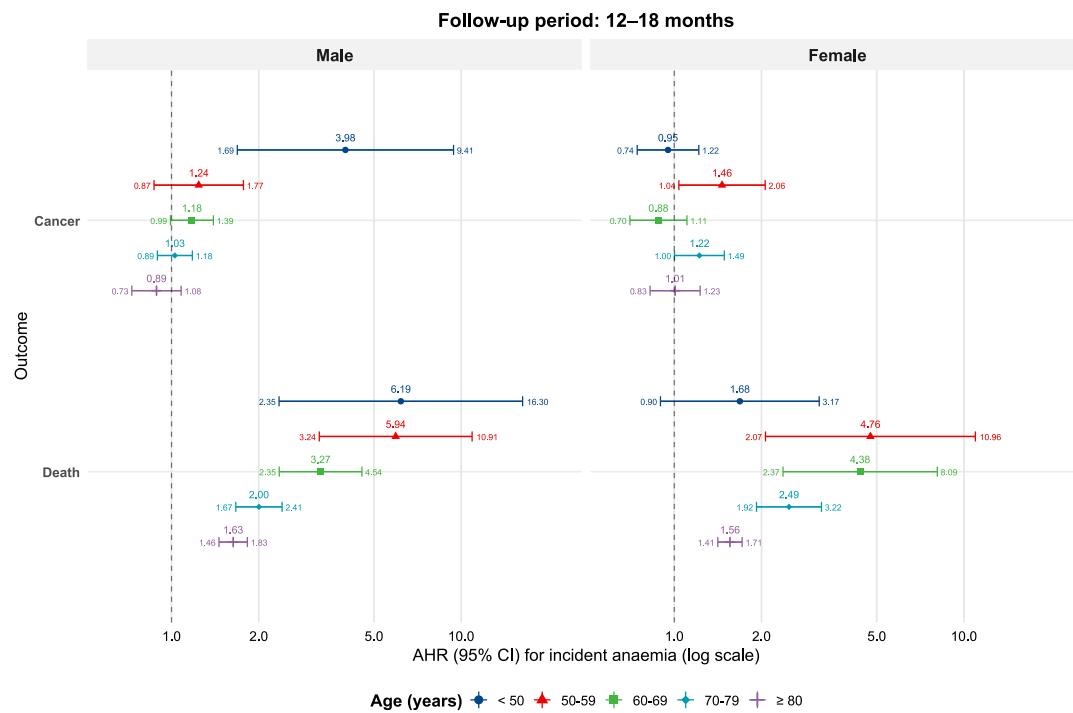


Figure S3d. Adjusted hazard ratios (AHRs) with 95% confidence intervals (CIs) for incident anaemia (log scale) according to sex and age group at 12–18 months follow-up. The results are adjusted for Charlson comorbidity index (CCI) value (points), healthcare contact frequency (HCF), mean corpuscular volume (MCV) class, and age (years).