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ORIGINAL ARTICLE

Patient profile and outcomes associated with follow-up in specialty vs. primary care in heart failure

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Abstract

Aims Factors influencing follow-up referral decisions and their prognostic implications are poorly investigated in patients with heart failure (HF) with reduced (HFrEF), mildly reduced (HFmrEF), and preserved (HFpEF) ejection fraction (EF). We assessed (i) the proportion of, (ii) independent predictors of, and (iii) outcomes associated with follow-up in specialty vs. primary care across the EF spectrum.

Methods and results We analysed 75 518 patients from the large and nationwide Swedish HF registry between 2000–2018. Multivariable logistic regression models were fitted to identify the independent predictors of planned follow-up in specialty vs. primary care, and multivariable Cox models to assess the association between follow-up type and outcomes. In this nationwide registry, 48 115 (64%) patients were planned for follow-up in specialty and 27 403 (36%) in primary care. The median age was 76 [interquartile range (IQR) 67–83] years and 27 546 (36.5%) patients were female. Key independent predictors of planned follow-up in specialty care included optimized HF care, that is follow-up in a nurse-led HF clinic [odds ratio (OR) 4.60, 95% confidence interval (95% CI) 4.41–4.79], use of HF devices (OR 3.99, 95% CI 3.62–4.40), beta-blockers (OR 1.39, 95% CI 1.32–1.47), renin–angiotensin system/angiotensin-receptor-neprilysin inhibitors (OR 1.21, 95% CI 1.15–1.27), and mineralocorticoid receptor antagonists (OR 1.31, 95% CI 1.26–1.37); and more severe HF, that is higher NT-proBNP (OR 1.13, 95% CI 1.06–1.20) and NYHA class (OR 1.13, 95% CI 1.08–1.19). Factors associated with lower likelihood of follow-up in specialty care included older age (OR 0.29, 95% CI 0.28–0.30), female sex (OR 0.89, 95% CI 0.86–0.93), lower income (OR 0.79, 95% CI 0.76–0.82) and educational level (OR 0.77, 95% CI 0.73–0.81), higher EF [HFmrEF (OR 0.65, 95% CI 0.62–0.68) and HFpEF (OR 0.56, 95% CI 0.53–0.58) vs. HFrEF], and higher comorbidity burden, such as presence of kidney disease (OR 0.91, 95% CI 0.87–0.95), atrial fibrillation (OR 0.85, 95% CI 0.81–0.89), and diabetes mellitus (OR 0.92, 95% CI 0.88–0.96). A planned follow-up in specialty care was independently associated with lower risk of all-cause [hazard ratio (HR) 0.78, 95% CI 0.76–0.80] and cardiovascular death (HR 0.76, 95% CI 0.73–0.78) across the EF spectrum, but not of HF hospitalization (HR 1.06, 95% CI 1.03–1.10).

Conclusions In a large nationwide HF population, referral to specialty care was linked with male sex, younger age, lower EF, lower comorbidity burden, better socioeconomic environment and optimized HF care, and associated with better survival across the EF spectrum. Our findings highlight the need for greater and more equal access to HF specialty care and improved quality of primary care.

Keywords Heart failure; Quality and outcomes; Risk factors; Disparities; Follow-up referrals

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Introduction

Heart failure (HF) is a common syndrome affecting 2–3% of the population.[1,2] Its prevalence increases with age, approximating 16% with age ≥80 years.[2] Despite significant advances in treatment over the last decades, HF remains associated with high morbidity and mortality.[3] Besides the impact on patients' prognosis and quality of life, the growing costs attributable to HF correspond to 1–2% of the total health care system expenditures in Europe.[4,5]

European guidelines identify follow-up of patients with HF as an understudied area.[6] Patients with HF, regardless of ejection fraction (EF), are recommended to receive regular, long-term follow-up to monitor symptoms, ensure optimized therapy, and foster the early identification of need for changes in management by the American and European guidelines on HF.[6,7] Depending on local organizations and patients' needs, follow-up can occur in specialty (e.g. cardiology and internal medicine) or primary care. According to the American guidelines on HF new-onset HF, persistent or worsening HF symptoms, and the inability to tolerate first-line HF treatments on optimal doses should be important triggers to referral to specialty care.[7] The European guidelines encourage multidisciplinary care management programmes in patients with HF (class of recommendation I, level of evidence A),[6] which might be difficult to achieve in primary care. Potential obstacles to the care of patients with HF in primary care might include delays between the worsening of HF symptoms or the onset of complications and the necessary diagnostic/interventional procedures, slow optimization of HF evidence-based treatments and doses, and late identification of patients requiring HF devices or referral for advanced interventions.[8]

Factors influencing follow-up referral decisions in everyday clinical practice have not been extensively investigated. Furthermore, there are limited data on the prognostic implications of the different types of follow-up in patients with HF, and especially according to specific EF phenotypes, that is, HF with reduced (HFrEF), mildly reduced (HFmrEF), and preserved EF (HFpEF).

Therefore, we aimed to assess (i) the proportion of, (ii) the independent predictors of, and (iii) outcomes associated with follow-up in specialty vs. primary care in a large and unselected HF population, with a focus on the different EF phenotypes and cause-specific outcomes.

Methods

Data sources

The Swedish HF (SwedeHF) registry has been previously described.[9] Briefly, SwedeHF is an ongoing nationwide registry that has enrolled patients from mainly secondary care in-patient and out-patient wards and clinics, but also from primary care to some extent, in Sweden since 11 May 2000. Until April 2017, the only inclusion criterion was clinician-judged HF, and thereafter a diagnosis of HF according to the International Statistical Classification of Diseases, Tenth Revision (ICD-10) codes I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0, and I13.2. During an outpatient clinic visit or at hospital discharge, data for approximately 80 variables, that is demographics, clinical characteristics, comorbidities, biomarkers, treatments, and use of care, are collected.

For the current analysis, SwedeHF was linked with Statistics Sweden, which provided socioeconomic data; the Swedish National Patient Registry, which provided additional comorbidities and the outcome HF hospitalization according to ICD-10 codes; and the Cause of Death Registry, which provided all-cause and cardiovascular (CV) mortality data. The linkage of all the above-mentioned data sources was performed through the personal identification number that all residents in Sweden, regardless of citizenship, have.

The initiation of SwedeHF and linkage with the aforementioned registries were approved by a multisite ethical committee. Individual consent was not required, but patients were informed of entry into SwedeHF and able to opt-out.

Patients

In the present analysis, patients with available data on EF and planned follow-up in specialty or primary care registered in SwedeHF between 2000 and 2018 were included. Follow-up type was defined as it was planned at the index date, that is registration in SwedeHF. HFrEF, HFmrEF, and HFpEF were defined according to the 2016 European guidelines on HF, as with EF $<$ 40%, 40 to 49%, and ≥50%, respectively.[10] For patients with $>$1 registration in SwedeHF, the last recording was used to better represent contemporary care. A flowchart depicting the patient selection is reported in the *Supporting information*, *Figure S1*. Index date was defined as the date of the outpatient visit or hospital discharge. Patients were censored at death/emigration, 5 years after the index date, or at the end of the study follow-up, that is 31st December 2019, whichever came first.

Statistical analyses

Baseline characteristics and missing data

Patient characteristics were compared in patients planned for follow-up in specialty vs. primary care by Kruskal–Wallis or ANOVA, as appropriate, if continuous, or χ^2 test if categorical. In multivariable models, missing data for baseline characteristics were handled by multiple imputation (15 imputed sets, 15 iterations, R-package: *mice*) stratified by EF phenotype.[11]

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The imputation models included all the variables marked with superscript a ([a]) in *Table 1*, follow-up type (i.e. specialty vs. primary care), and the outcome all-cause mortality as Nelson–Aalen estimate.

Independent predictors of follow-up type Variables labelled with a superscript b ([b]) in *Table 1* were included as covariates in a multivariable logistic regression model with planned follow-up type as a dependent variable to identify patient characteristics independently associated with follow-up type. Results were reported as odds ratio (OR) with 95% confidence intervals (CIs). We fitted further models stratifying by EF phenotype, which included the variables labelled with a superscript a ([a]) in *Table 1*.

Outcome analysis

Outcomes were risk of all-cause death, CV death, and first HF hospitalization. Survival functions were estimated by the Kaplan–Meier method. Event-rates per 100 patient-years with 95% CI were compared across the follow-up types by exact Poisson test. The independent association between planned follow-up type and outcomes was assessed by multivariable Cox proportional hazards models including as covariates all the variables labelled with a superscript b ([b]) in *Table 1*. Results were reported as hazard ratio (HR) with 95% CI. The proportional hazards assumption was assessed visually by Schoenfeld residuals and met. To assess whether the association of planned follow-up type with outcomes was consistent across relevant subgroups, that is HFpEF vs. HFmrEF vs. HFrEF, age $<$75 vs. $\geq$75 years, male vs. female patients, university vs. no university education, cohabitating vs. single living, NYHA I–II vs. III–IV, N-terminal pro-B-type natriuretic peptide (NT-proBNP) $<$median vs. $\geq$median, mean arterial pressure $<$90 vs. $\geq$90 mmHg, and by presence vs. no presence of atrial fibrillation, diabetes mellitus, chronic obstructive pulmonary disease, and kidney disease, separate fully adjusted Cox proportional hazards models including an interaction term between each subgroup variable and planned follow-up type were fitted with statistical significance for interaction assessed by Wald test.

A P value $<$0.05 was considered statistically significant. All analyses were performed using the statistical software R version 4.0.4. A more detailed description of variable definitions is available in *Table S1*.

Results

Patient characteristics

Of 75 518 patients included in the study, 39 625 (52.5%) had HFrEF, 17 728 (23.5%) had HFmrEF, and 18 225 (24.1%) had HFpEF. The median age was 76 (interquartile range [IQR] 67–83) years in the overall study population, rising with EF (median age 74 [IQR 66–82], 76 [IQR 67–83], and 79 [IQR 72–85] years in HFrEF, HFmrEF, and HFpEF, respectively). In the overall population, 27 546 (36.5%) were female, with less female patients in HFrEF (28.7%) vs. HFmrEF (37.6%) vs. HFpEF (52.2%). In our study population, 48 115 (63.7%) and 27 403 (36.3%) patients were planned for follow-up in specialty and primary care, respectively (*Table 1*). Referral to specialty care was more common in patients with HFrEF (72.6%) than HFmrEF (60.0%) and HFpEF (47.8%). Patients referred to specialty care were also younger, more frequently male, cohabitating, with higher income and education levels, lower EF, shorter history of HF, and fewer comorbidities. Patient characteristics stratified by EF phenotype showed differences according to the follow-up types which were overall consistent with the unstratified analysis (*Tables S2–S4*).

Independent predictors of follow-up type

Differences in patient characteristics reported in *Table 1* are unadjusted. Therefore, we performed multivariable logistic regression models to identify the patient characteristics independently associated with follow-up type. Patients with HFrEF vs. HFmrEF vs. HFpEF were more likely to be planned for a follow-up in specialty vs. primary care. Other independent predictors of planned follow-up in specialty care included referral to follow-up in a nurse-led HF unit, use of HF devices (cardiac resynchronization therapy or implantable cardioverter-defibrillator) and treatment with guidelines-recommended HF medications [renin–angiotensin-system inhibitors (RASi)/angiotensin-receptor-neprilysin inhibitors (ARNi), beta-blockers, and mineralocorticoid receptor antagonists (MRA), more severe HF [i.e. higher New York Heart Association (NYHA) class and N-terminal pro-B-type natriuretic peptides (NT-proBNP) and lower blood pressure], and valvular disease (*Figure 1*).

Conversely, patients planned for follow-up in primary care were more likely older, female, with longer HF duration and factors linked with lower socioeconomic status (living alone, lower education level, and lower income). They also had higher comorbidity burden (e.g. kidney disease, atrial fibrillation, diabetes mellitus, hypertension, and chronic obstructive pulmonary disease) and were more likely to receive diuretics. Ischaemic heart disease and anaemia were among the characteristics not associated with follow-up type.

Independent predictors of planned follow-up were overall consistent within each EF phenotype (*Figures S2–S4*).

Outcome analysis

Over a median follow-up time of 2.64 (IQR 1.23–5.00) years until event or censoring, 33 542 (44.4%) patients died from any cause, and 20 836 (27.6%) died of CV causes, and

Table 1 Patient characteristics at baseline, stratified by follow-up type

	Specialty care 48 115 (63.7%)	Primary care 27 403 (36.3%)	*P*	Missing
Sociodemographic data				
Index year[a,b]			<0.001	0.0%
2000–2011	16 555 (34.4%)	12 324 (45.0%)		
2012–2018	31 560 (65.6%)	15 079 (55.0%)		
Female[a,b]	14 995 (31.2%)	12 551 (45.8%)	<0.001	0.0%
Age, years	71 (±12)	80 (±9)	<0.001	0.0%
≥75 years[a,b]	20 522 (42.7%)	21 259 (77.6%)	<0.001	0.0%
Income level			<0.001	0.2%
Lowest tertile	15 533 (32.4%)	11 773 (43.0%)	<0.001	0.2%
Medium tertile	16 642 (34.7%)	10 904 (39.8%)		
Highest tertile	15 830 (33.0%)	4706 (17.2%)		
Income level: Lowest tertile[a,b]	15 533 (32.4%)	11 773 (43.0%)	<0.001	0.2%
Education level			<0.001	2.1%
Compulsory school	18 799 (39.8%)	14 633 (54.9%)		
Secondary school	19 680 (41.6%)	8849 (33.2%)		
University	8791 (18.6%)	3148 (11.8%)		
Education level: Secondary school or less[a,b]	38 479 (81.4%)	23 482 (88.2%)	<0.001	2.1%
Living alone[a,b]	21 064 (43.9%)	15 674 (57.2%)	<0.001	0.2%
Children[a,b]	39 983 (83.4%)	23 087 (84.2%)	<0.001	0.0%
Clinical data				
EF phenotype[b]			<0.001	0.0%
HFrEF	28 743 (59.7%)	10 822 (39.5%)		
HFmrEF	10 663 (22.2%)	7065 (25.8%)		
HFpEF	8709 (18.1%)	9516 (34.7%)		
Follow-up in nurse-led HF unit[a,b]	30 838 (65.4%)	7003 (26.1%)	<0.001	2.0%
Caregiver: in-patient[a,b]	15 537 (32.3%)	14 696 (53.6%)	<0.001	0.0%
HF duration ≥6 months[a,b]	25 485 (54.2%)	17 992 (67.3%)	<0.001	2.4%
NYHA III–IV[a,b]	14 571 (39.4%)	7732 (43.2%)	<0.001	27.3%
Body mass index, kg/m^2	27 (±6)	27 (±6)	<0.001	42.0%
≥30 kg/m^2[a,b]	7503 (26.3%)	3752 (24.6%)	<0.001	42.0%
Mean arterial pressure, mmHg	90 (±13)	91 (±13)	<0.001	1.8%
<90 mmHg[a,b]	22 912 (48.5%)	11 938 (44.3%)	<0.001	1.8%
Heart rate, b.p.m.	73 (±15)	74 (±15)	<0.001	4.5%
≥70 b.p.m.[a,b]	25 461 (55.2%)	15 600 (59.9%)	<0.001	4.5%
eGFR, mL/min/1.73 m^2	64 [46, 82]	53 [38, 70]	<0.001	1.8%
Haemoglobin, g/L	133 (±18)	129 (±17)	<0.001	5.4%
Potassium, mmol/L	4 (±0)	4 (±0)	<0.001	20.3%
NT-proBNP, pg/L	2125 [854, 4860]	2440 [1032, 5860]	<0.001	47.8%
≥median (by EF phenotype)[a,b]	12 529 (47.2%)	7175 (55.9%)	<0.001	47.8%
Comorbidities				
Peripheral artery disease[a,b]	4428 (9.2%)	2693 (9.8%)	0.005	0.0%
Stroke/transitory ischaemic attack[a,b]	7127 (14.8%)	5883 (21.5%)	<0.001	0.0%
Anaemia[a,b]	14 857 (33.0%)	10 789 (40.8%)	<0.001	5.4%
Depression[a,b]	1799 (3.7%)	1168 (4.3%)	<0.001	0.0%
Cancer past 3 years[a,b]	6770 (14.1%)	4259 (15.5%)	<0.001	0.0%
Liver disease[a,b]	1180 (2.5%)	484 (1.8%)	<0.001	0.0%
Major bleeding[a,b]	8501 (17.7%)	5816 (21.2%)	<0.001	0.0%
Kidney disease[a,b]	20 938 (44.3%)	16 579 (61.7%)	<0.001	1.8%
Diabetes mellitus[a,b]	12 924 (26.9%)	8141 (29.7%)	<0.001	0.0%
Atrial fibrillation[a,b]	26 359 (54.8%)	17 359 (63.3%)	<0.001	0.0%
Hypertension[a,b]	29 951 (62.2%)	19 607 (71.6%)	<0.001	0.0%
Chronic obstructive pulmonary disease[a,b]	6131 (12.7%)	4453 (16.3%)	<0.001	0.0%
Ischaemic heart disease[a,b]	26 112 (54.3%)	15 538 (56.7%)	<0.001	0.0%
Valvular disease[a,b]	10 747 (22.3%)	5402 (19.7%)	<0.001	0.0%
Charlson comorbidity index	2 [1, 4]	3 [2, 5]	<0.001	0.0%
Treatments				
Beta-blockers[a,b]	43 888 (91.4%)	22 891 (83.7%)	<0.001	0.2%
RASi/ARNi[a,b]	42 338 (88.7%)	20 775 (76.6%)	<0.001	0.9%
MRA[a,b]	18 944 (39.5%)	7981 (29.3%)	<0.001	0.5%
Diuretics[a,b]	35 330 (73.7%)	22945 (84.0%)	<0.001	0.3%
Digoxin[a,b]	6539 (13.6%)	4140 (15.2%)	<0.001	0.3%
Nitrates[a,b]	5534 (11.5%)	5108 (18.7%)	<0.001	0.4%
Anticoagulants[a,b]	23 279 (48.5%)	11 677 (42.8%)	<0.001	0.3%

(*Continues*)

Table 1 (continued)

	Specialty care 48 115 (63.7%)	Primary care 27 403 (36.3%)	*P*	Missing
Antiplatelets[a,b]	19 579 (40.8%)	12 059 (44.2%)	<0.001	0.4%
Statins[a,b]	24 841 (51.7%)	11 429 (41.8%)	<0.001	0.3%
HF device[a,b]	5537 (11.5%)	562 (2.1%)	<0.001	1.4%

Abbreviations: ARNi, angiotensin-receptor-neprilysin inhibitor; b.p.m, beats per minutes; EF, ejection fraction; eGFR, estimated glomerular filtration rate (calculated by Chronic Kidney Disease Epidemiology Collaboration formula); HF, heart failure; HF device, heart failure device (cardiac resynchronization therapy or implantable cardioverter-defibrillator); HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class; RASi, renin–angiotensin-system inhibitor.
Summary statistics based on unimputed data. Data are presented as absolute (relative) frequencies, mean (±standard deviations), and median [interquartile range], and compared by χ^2-test, ANOVA, and Kruskal–Wallis test, respectively.
[a]Labelled variables were included in the multiple imputation models together with follow-up type, all-cause mortality and Nelson–Aalen estimator.
[b]Labelled variables were included in the adjusted Cox proportional hazards models and the overall logistic regression model assessing independent predictors of follow-up type.

22 716 (30.1%) were hospitalized for HF. Crude event rates for all outcomes were lower in patients followed-up in specialty vs. primary care across the EF spectrum, and are shown in *Table 2*, with Kaplan–Meier curves depicted in *Figure 2*.

Follow-up in specialty vs. primary care was associated with 50% lower crude risk of all-cause mortality (HR 0.50, 95% CI 0.49–0.51) and with 22% lower risk of outcome after adjusting for demographics, socioeconomics, clinical and organizational variables, comorbidities, and treatments (HR 0.78, 95% CI 0.76–0.80) (*Figure 3*).

For CV mortality, follow-up in specialty vs. primary care was associated with 52% lower crude risk (HR 0.48, 95% CI 0.46–0.49) and with 24% lower risk of outcome after full adjustments (HR 0.76, 95% CI 0.73–0.78) (*Figure 3*).

Follow-up in specialty vs. primary care was associated with 13% lower crude risk of first HF hospitalization (HR 0.87, 95% CI 0.85–0.90) but 6% higher risk after full adjustments (HR 1.06, 95% CI 1.03–1.10) (*Figure 3*). For all the outcomes, a considerable part of the difference in HR in crude vs. adjusted analyses was explained by differences in demographics followed by clinical characteristics of patients receiving follow-up in specialty vs. primary care.

Follow-up in specialty care was associated with lower all-cause (*Figure 4*) and CV mortality (*Figure S5*) across all analysed subgroups. The association with lower all-cause mortality was consistent regardless of the EF phenotype, age, sex, marital status, and blood pressure, but the magnitude was greater in patients with university vs. no university education (interaction *P* value 0.01), NYHA I–II vs. III–IV (interaction *P* value <0.001), NT-proBNP <median vs. ≥median (interaction *P* value <0.001), and those without vs. with atrial fibrillation (interaction *P* value <0.001), diabetes mellitus (interaction *P* value <0.001), chronic obstructive pulmonary disease (interaction *P* value <0.001), and kidney disease (interaction *P* value <0.001). Risk of HF hospitalization was higher with referral to specialty care in HFrEF, whereas there was no significant association in HFmrEF and HFpEF (interaction *P* value <0.001) (*Figure S6*).

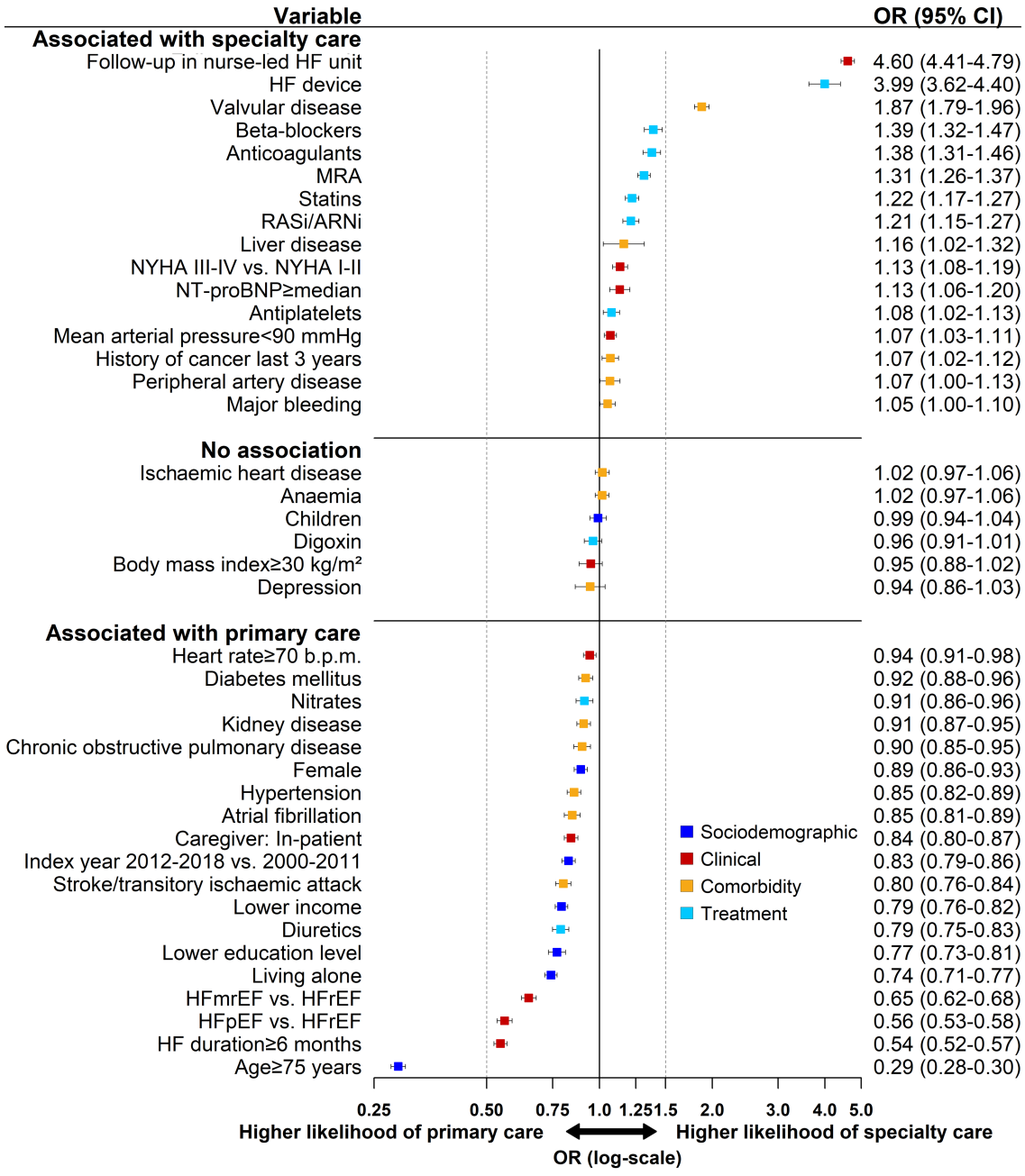
Discussion

In this analysis of a large and unselected nationwide HF population registered as in-hospital or out-patients, two-thirds of patients were referred for follow-up in specialty care whereas one-thirds in primary care. Factors independently associated with specialty care referral included younger age, male sex, higher socioeconomic status, lower EF and more severe HF, fewer comorbidities, and overall more optimized HF care, including HF nurse team visits. Referral to specialty care was associated with lower risk of all-cause and CV mortality, but higher risk of HF hospitalization. The observed associations between planned follow-up type and outcomes were only partially explained by the differences in the analysed patient characteristics.

Use of specialty vs. primary care follow-up

Data on follow-up in specialty vs. primary care from large HF populations are overall limited, with a few studies suggesting low use of specialized follow-up across different health care systems.[12,13] In a previous study using electronic health records from the Stockholm region, 43% of patients with HF were seen in a specialist outpatient clinic between 1997 and 2010.[14] Referral to specialty care follow-up in our more contemporary nationwide SwedeHF population was higher, which might reflect primary care physicians' difficulties in coordinating the increasing complexity of contemporary HF care, including new pharmacotherapies, catheter-based procedures, and device or surgical therapies.[15,16] A novelty of our study is the assessment of referral patterns across the

Figure 1 Independent odds ratios for follow-up in specialty vs. primary care. Multivariable logistic regression model with follow-up in specialty vs. primary care as dependent variable. Abbreviations: ARNi, angiotensin-receptor-neprilysin inhibitor; b.p.m, beats per minutes; CI, confidence interval; HF, heart failure; HF device, heart failure device (cardiac resynchronization therapy or implantable cardioverter-defibrillator); HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class; OR, odds ratio; RASi, renin–angiotensin-system inhibitor.



EF spectrum. In our population, three-fourths of patients with HFrEF vs. one-half of those with HFpEF were referred to specialty care. We suggest that this is low for both groups, given that all patients with HF need continuous risk factor and symptom management, and in particular in HFrEF, where there are extensive complex evidence-based interventions.

A recent hospital admission for HF highlights the need for closer monitoring and treatment optimization. Therefore,

Table 2 Event rates according to follow-up type in the overall study population and stratified by EF

	Specialty care	Primary care	*P* value
	Events/100 patient-years (95% CI)		
All-cause mortality	11.9 (11.7–12.1)	24.5 (24.1–24.9)	<0.001
HFrEF	12.1 (11.9–12.3)	28.5 (27.8–29.2)	<0.001
HFmrEF	10.3 (10.0–10.7)	21.4 (20.7–22.1)	<0.001
HFpEF	13.2 (12.8–13.7)	22.7 (22.1–23.3)	<0.001
Cardiovascular mortality	7.2 (7.1–7.3)	15.6 (15.3–15.9)	<0.001
HFrEF	7.8 (7.6–8.0)	19.5 (19.0–20.1)	<0.001
HFmrEF	5.7 (5.4–6.0)	13.2 (12.7–13.7)	<0.001
HFpEF	7.1 (6.8–7.5)	13.4 (12.9–13.9)	<0.001
First HF hospitalization	11.9 (11.7–12.1)	14.6 (14.2–14.9)	<0.001
HFrEF	13.9 (13.6–14.2)	18.4 (17.8–19.0)	<0.001
HFmrEF	8.2 (7.9–8.5)	12.2 (11.6–12.7)	<0.001
HFpEF	10.6 (10.1–11.0)	12.5 (12.0–13.0)	<0.001

Abbreviations: CI, confidence interval; EF, ejection fraction; HF, heart failure; HFmrEF, HF with mildly reduced EF; HFpEF, HF with preserved EF; HFrEF, HF with reduced EF.

previous analyses showing 57% of patients hospitalized for HF being discharged to follow-up in primary care,[17] together with our data reporting that more than half of the patients planned for follow-up in primary care came from an in-patient setting, may indicate inappropriate referral and the need of clearer guidance on HF management.

Independent predictors of planned follow-up in specialty vs. primary care

In the current analysis, patients who were younger, male, had HFrEF, more severe HF, and lower comorbidity burden were more likely referred to specialty care. Similar patterns have been observed for the use of nurse-led HF outpatient clinics and overall optimal HF care in Sweden,[18,19] but also in very different healthcare systems, for example, the USA.[20] Altogether, these findings may indicate that physicians perceive specialized HF care to be of greater benefit or more justified in younger patients with HFrEF and fewer comorbidities, that is, a similar scenario as in HF randomized controlled trials. However, our data do not support this potential perception because referral to specialty care had an association with better survival after adjustments for these and many other variables, which was consistent regardless of EF and many other patients, although the magnitude of the association was slightly greater in patients with mild vs. severe HF, and slightly smaller in patients with vs. without comorbidities (atrial fibrillation, diabetes mellitus, chronic obstructive pulmonary disease, and kidney disease). General frailty and the presence of comorbidities is common in HF,[1] may negatively impact symptoms, quality-of-life, and prognosis, affect the timely recognition of worsening HF, and is often associated with undertreatment.[21–23] Therefore, one might argue that these patient characteristics should rather encourage follow-up in specialty care where a stricter and more structured follow-up might foster an earlier identification and better management of potential side effects, leading to a safer and greater use of HF therapies. Consistently, our and previous data show that optimal HF management with evidence-based therapy is more likely achieved in patients followed-up in specialty care,[24,25] whereas HF treatment might be more likely limited to treating symptoms with diuretics in primary care,[25] despite the notion that patients without optimized HF therapy ought to be even less suitable for follow-up in primary care.

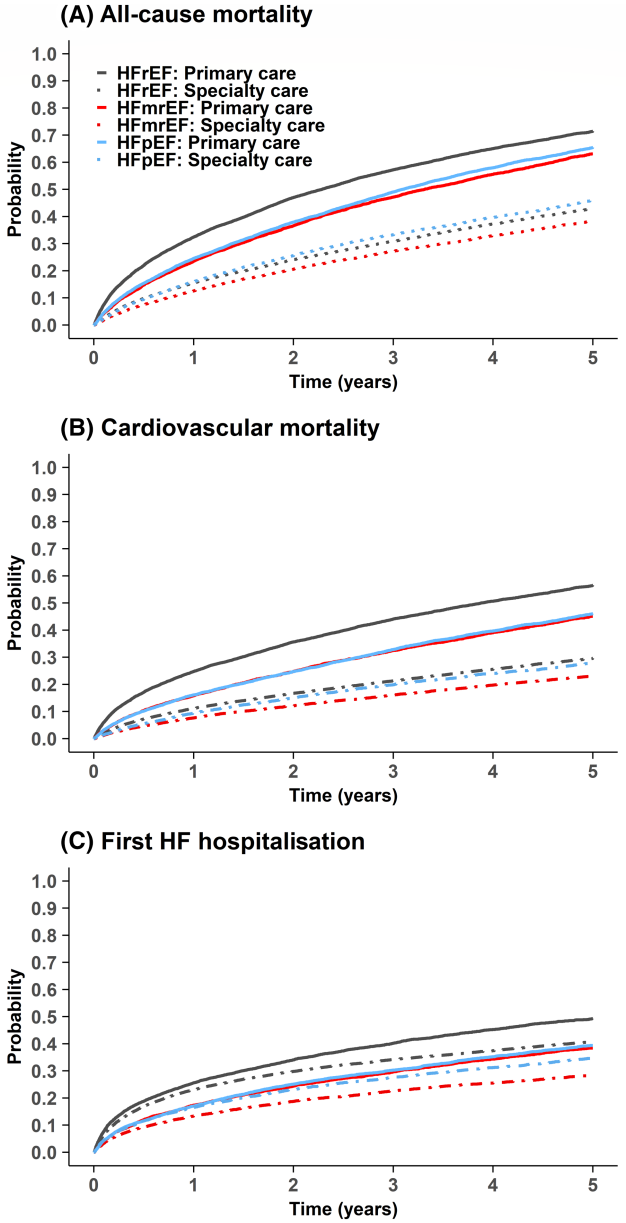
Lower socioeconomic status is associated with worse prognosis in HF.[26] This link may involve differences in lifestyle, treatment adherence, health literacy, and inequalities in provided healthcare including prescription and referral patterns.[27] In a universal healthcare system, we identified three indicators of lower socioeconomic status (lower income, education level, and single living) independently associated with lower likelihood of referral to specialty care. This is consistent with previous studies showing less optimized HF care in these patients.[19,26] Factors such as the geographical distribution of specialty care clinics and the small fee paid upon drug dispensation and health care visits may still represent a limitation to the access to specialty care and adherence to specialists' recommendations.

Outcomes in specialty vs. primary care

Previous studies showed lower all-cause mortality in patients with HFrEF upon hospital discharge, and outpatients with EF $>$ 40% if followed-up in specialty care.[28,29] In contrast, in 2007 a randomized trial enrolling patients with HF to cardiologist or general practitioner follow-up did not find any difference in mortality or hospitalization.[24]

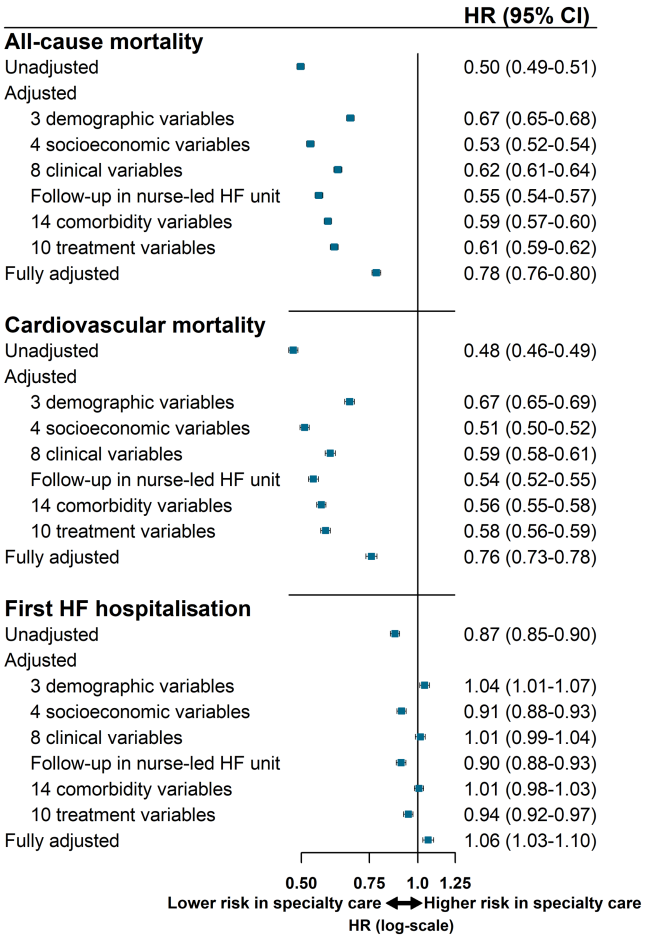
In the present study, analysing $>$70 000 patients with HF across the EF spectrum, a planned follow-up in specialty care was strongly associated with lower risk of all-cause and CV mortality even after extensive adjustments, and consistently across the EF phenotypes. Differences in demographic and

Figure 2 Kaplan–Meier curves for all-cause mortality (A), cardiovascular mortality (B), and first HF hospitalization (C). Abbreviations: EF, ejection fraction; HF, heart failure; HFmrEF, HF with mildly reduced EF; HFpEF, HF with preserved EF; HFrEF, HF with reduced EF.



clinical variables explained most of the better crude survival observed in patients with follow-up in specialty vs. primary care. There was nevertheless considerable residual difference in outcomes between follow-up types. This might be at least partially explained by better management of comorbidities like atrial fibrillation, valvular diseases, and iron deficiency, early reporting of symptoms, and self-management, for example, for adjustments of diuretic use, in specialty care. A follow-up in specialty care may also entail closer monitoring, which would allow earlier detection of worsening HF and therefore earlier hospital admission. Consistently, referral to specialty care was paradoxically associated with higher risk of first HF hospitalization after extensive adjustments. While HF hospitalization contributes to the health-economic burden of HF,[4] when necessary, an earlier hospital admission might prevent death in patients with worsening HF. Interestingly, similar patterns were previously observed with referral to HF nurse teams, which was associated with lower risk of mortality but not HF hospitalization.[18] However, earlier hospitalizations may not necessarily imply more hospitalizations, and

Figure 3 Association between follow-up type and risk of outcomes. Cox proportional hazards regression models with step-wise adjustments. Demographics include index year (2000–2011 vs. 2012–2018), age (<75 vs. ≥75), sex. Socioeconomics include income level (lowest tertile vs. upper two tertiles), education level (university vs. secondary school or less), living alone, children. Clinical characteristics include: ejection fraction phenotype, caregiver (in-patient vs. out-patient), heart failure duration ≥6 months, New York Heart Association functional class (I–II vs. III–IV), body mass index (<30 vs. ≥30), mean arterial pressure (<90 vs. ≥90), heart rate (<70 vs. ≥70), N-terminal pro-B-type natriuretic peptide (<median vs. ≥median). Comorbidities include peripheral artery disease, stroke/transitory ischaemic attack, anaemia, depression, cancer last 3 years, liver disease, major bleeding, kidney disease, diabetes mellitus, atrial fibrillation, hypertension, chronic obstructive pulmonary disease, ischaemic heart disease, and valvular disease. Treatments include beta-blockers, renin–angiotensin-system inhibitor/angiotensin-receptor-neprilysin inhibitor, mineralocorticoid receptor antagonist, diuretics, digoxin, nitrates, anticoagulants, antiplatelets, statins, heart failure device treatment with cardiac resynchronization therapy, or implantable cardioverter-defibrillator. Abbreviations: CI, confidence interval; HF, heart failure; HR, hazard ratio.

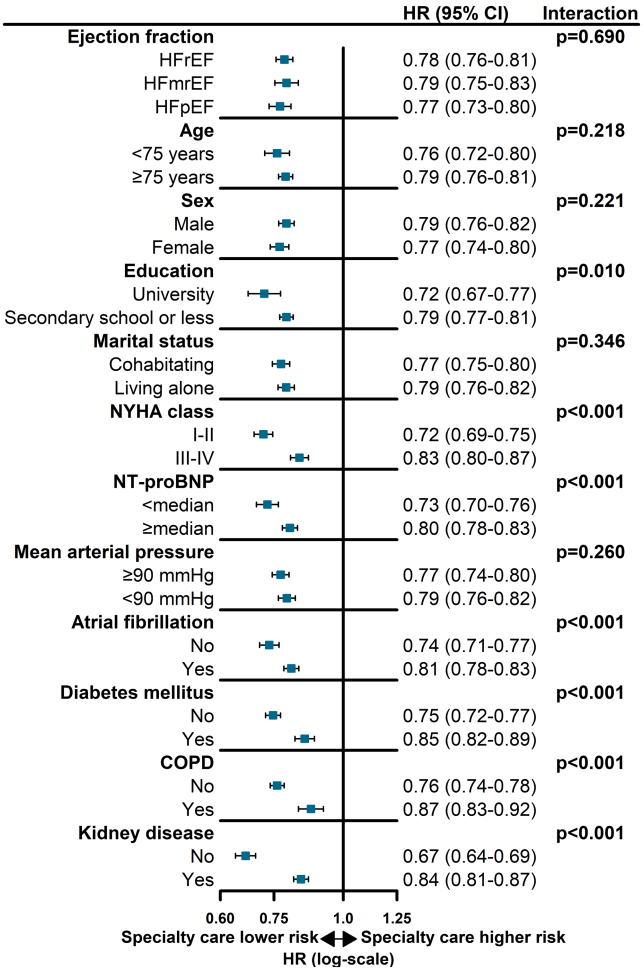


a recent study showed greater treatment use and lower re-hospitalization rates for HF following the implementation of a HF clinic based organizational programme.[30]

Strengths and limitations

A strength of the current study is the use of a large, contemporary, and well-characterized nationwide cohort, which enabled a large sample size, separated analyses for the different EF phenotypes and different outcomes, and comprehensive adjustments. As in any observational study, residual confounding cannot be ruled out. Differences in patient characteristics other than those collected in SwedeHF might explain the difference in outcomes linked with follow-up type, rather than a different performance of specialty vs. primary care. Follow-up was assessed as planned at the index date, and as in an intention-to-treat trial protocol, this does not guarantee that the patient subsequently underwent or maintained the type of follow-up defined at the index date. Patients in SwedeHF are better treated and have better prognosis than patients not enrolled in the registry.[31] SwedeHF has much higher coverage in secondary vs. primary care, with patients encountered in secondary care being more likely to continue a follow-up in the same setting. Centres enrolling patients in SwedeHF are less likely located in rural areas

Figure 4 Association between follow-up type and risk of death in clinically relevant subgroups. Cox proportional hazards regression models adjusted for variables labelled with a superscript a ([a]) in *Table 1*, including an interaction term between the subgroup variable and follow-up type. Abbreviations: CI, confidence interval; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide.



where hospital access might be more limited. These factors might limit the external validity of our results and lead to overestimate the proportion of patients receiving specialized follow-up. Although most of the variables had no or a very limited amount of missing values, NT-proBNP, NYHA class, and body mass index had until 48% missing data. While multiple imputation has been shown to yield unbiased estimates even in the setting of high degrees of missingness and to increase external validity, we cannot exclude the possibility that missing data influenced our findings. Finally, the SwedeHF broad inclusion criteria, while improving generalizability, might lead to some risk of misdiagnosis, in particular in patients classified as with HFpEF. The validity of ICD-coding for an HF diagnosis in Sweden is 88% when an echocardiographic assessment is present, as was the case for all patients included in this study.[32]

Conclusions

In a large and contemporary nationwide HF population, two-thirds were planned for referral to specialty care. Patients referred to specialty care were younger, more likely male, had higher socioeconomic status, lower EF, and more severe HF but less comorbidities, and were more likely to receive guideline-recommended HF therapies. Referral to specialty care was independently associated with better survival but paradoxically higher risk of first HF hospitalization, suggesting that rigorous monitoring may entail earlier hospitalizations that avert subsequent death.

Our findings highlight the need to enable better identification of patients in need of follow-up in specialty care, for public health strategies to avoid unjustified inequalities in re-

ferrals, and to improve the use of guideline-recommended HF treatments in primary care.

Conflict of interest

G. S. reports grants and personal fees from Vifor, grants and non-financial support from Boehringer Ingelheim, personal fees from Società Prodotti Antibiotici, grants and personal fees from AstraZeneca, personal fees from Roche, personal fees from Servier, grants from Novartis, personal fees from GENESIS, personal fees from Cytokinetics, personal fees from Medtronic, grants from Boston Scientific, grants from PHARMACOSMOS, grants from Merck, outside the submitted work.

F. L. has nothing to disclose.

M. E. has nothing to disclose.

L. H. L reports research grants from AstraZeneca, Novartis, Boerhinger Ingelheim, Vifor-Fresenius, and Boston Scientific, and consulting or speaker's honoraria from AstraZeneca, Novartis, Boehringer Ingelheim, Vifor-Fresenius, Bayer, Sanofi, Merck, Myokardia, Orion Pharma, MedScape, Radcliffe Cardiology, Lexicon, and Respicardia, and stock ownership in AnaCardio, outside the submitted work.

C. L. reports consulting fees from AstraZeneca, Roche diagnostics and speaker Honoria from Novartis, Astra, Bayer, Medtronic, Impulse Dynamics and Vifor.

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G. R. has no conflict of interest related to the current work.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting Information.

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