



Editorial



Making the invisible visible: Leveraging electronic health records to uncover familial hypercholesterolemia in primary care[☆]

Familial hypercholesterolemia (FH) remains one of the most underdiagnosed and undertreated inherited disorders in modern cardiovascular medicine [1]. Early diagnosis and effective treatment are essential to reduce the lifetime burden of atherosclerotic cardiovascular disease (ASCVD) in affected individuals [2,3]. As most FH patients remain unidentified until a cardiovascular event occurs, primary care serves as a crucial platform for early case detection, treatment initiation, and referral for specialist evaluation.

Electronic health records (EHRs) provide an unprecedented opportunity to identify individuals with FH phenotypes in a systematic way. Algorithms based on low density lipoprotein cholesterol (LDL-C) thresholds, lipid-lowering therapy (LLT) status, and exclusion of secondary causes can help flag at-risk individuals who might otherwise remain undiagnosed. Incorporating these tools into routine primary care workflows can enable earlier diagnosis, improve treatment outcomes, and trigger cascade screening in family members. Leveraging primary care data not only improves case detection but also enables risk stratification and personalized management.

In their recent work published in *Atherosclerosis*, Gijón-Conde and colleagues [4] provide valuable insight into the clinical characteristics and management of FH phenotype in a large primary care population in Madrid. This cross-sectional study includes over 156,000 adults with available lipid profiles across 69 health centers and identifies FH phenotype using pragmatic criteria: untreated LDL-C ≥ 240 mg/dL (≥ 6.2 mmol/L) or ≥ 160 mg/dL (≥ 4.1 mmol/L) on LLT, with triglycerides < 200 mg/dL (< 2.3 mmol/L) and normal thyroid-stimulating hormone levels.

Among the total population, 6187 individuals (3.96 %) had severe hypercholesterolemia, and 1600 (1.03 %) met criteria for FH phenotype. This prevalence aligns with global estimates for heterozygous FH (HeFH), reinforcing the feasibility of EHR-based screening in real-world practice. These findings support the applicability of such phenotype-driven approaches to aid early identification in routine care.

Strikingly, none of the FH phenotype patients in this study had a formal FH diagnosis recorded, highlighting a critical diagnostic gap underscoring the urgency of incorporating EHR-driven case-finding tools in primary care. The majority were female, younger, and had fewer comorbidities than non-FH individuals. All treated FH patients had LDL-C levels above 130 mg/dL (> 3.4 mmol/L), highlighting persistent undertreatment and failure to reach guideline-recommended targets despite therapy.

Interestingly, the prevalence of prior ASCVD was lower among FH phenotype patients (8.6 %) than non-FH counterparts, despite higher LDL-C levels. Possible explanations include survivor bias, whereby individuals with FH who experienced early fatal events may be underrepresented, as well as differences in health-seeking behaviors or under-recognition. Moreover, some patients with FH may have developed premature ASCVD and were consequently referred to specialist care. The predominance of women (72.7 %) in the FH phenotype group may partly account for this pattern, given known sex-based differences in cardiovascular risk and care [5].

The relatively low ASCVD burden alongside a 97 % LLT usage rate—mostly for primary prevention—may reflect either effective risk reduction or selection bias favoring already-treated individuals. Inclusion criteria requiring lipid profiles may have unintentionally excluded patients managed elsewhere or without recent testing. The COVID-19 pandemic, overlapping with the January 2018–December 2021 study period, likely further limited routine healthcare access, lipid monitoring, or ASCVD diagnosis documentation [6].

1. Detection challenges and emerging tools for FH in primary care

While this study highlights the potential of EHR-based detection, FH identification in primary care remains inconsistent across the literature. Most real-world datasets lack the genetic or family history, and physical findings data necessary for scores like the Dutch Lipid Network Criteria (DLNC) [3,7,8], prompting interest in simplified tools using lipid values and prescription records. Algorithms such as FAMCAT [8,9] show promise in primary care EHR validation studies but require further validation. Current methods—including centralized lab screening and ICD/statin-based identification—lack broad consensus, and a 2021 Cochrane review confirmed insufficient high-quality evidence for any one strategy [10]. Given these gaps, LDL-C thresholds (e.g., ≥ 190 mg/dL [≥ 4.9 mmol/L] or ≥ 240 mg/dL [≥ 6.2 mmol/L]) are widely used for initial screening particularly when genetic or family history data are unavailable [11]. Importantly, in secondary prevention settings, the DLNC allocate three points for patients with premature myocardial infarction and LDL-C levels as low as 155 mg/dL (≥ 4.0 mmol/L),—enabling classification as “possible FH”. However, clinicians increasingly note that many treated patients lack classical physical signs reducing the DLNC’s utility [12]. This reinforces a shift toward

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phenotype- or algorithm-based detection strategies, using routinely available real-world clinical data [13].

The use of a cutoff of untreated LDL-C of ≥ 240 mg/dL (≥ 6.2 mmol/L), or on therapy ≥ 160 mg/dL (≥ 4.1 mmol/L), may have excluded well-controlled FH or capture non-monogenic cases. However, the triglyceride filter of >200 mg/dL (>2.3 mmol/L) is a strength, improving diagnostic precision by ruling out familial combined hyperlipidemia (FCHL) [14]—a common differential diagnosis that resembles FH but has distinct metabolic features. Previous studies such as those from the FHSC [15] collaboration did not include this exclusion, while the SAFEHEART [16] registry has incorporated similar criteria. This approach enhances the specificity of the FH phenotype identification in routine practice and contributes to a more accurate identification of monogenic FH candidates.

2. Sex and gender disparities in FH management

This study highlights notable sex-based disparities in FH care. Although women represented the majority of FH phenotype cases (72.7 %), they were less likely than men to receive high- or very high-intensity LLT (25.3 % vs. 36.6 %). While overall LLT use was higher among women, intensity remained suboptimal reflecting broader trends of delayed diagnosis and undertreatment in women. Women with FH often lose years of potential therapy due to pregnancy, lactation, and diagnostic inertia [5].

Importantly, both FH and non-FH patients had an average age around 60, suggesting many women were likely postmenopausal—a phase linked to worsening lipid profiles. However, menopausal status was not assessed, limiting interpretation of sex-related differences. Addressing these gaps requires greater awareness, systematic screening, and tailored care strategies across women's life stages to improve outcomes in FH.

3. Study limitations and Berkson bias in FH registries

As the authors acknowledge, this study has several limitations that affect its generalizability. Its retrospective design, lack of genetic confirmation, family history, and cardiovascular outcome data limit diagnostic precision. Only 16.8 % of the total population had lipid measurements, suggesting selection bias toward individuals already engaged in care. The COVID-19 pandemic (2018–2021) likely further restricted access to testing and routine follow-up.

Missing data on secondary causes (e.g., corticosteroid use), lifestyle, adherence, and provider-level barriers limit the interpretation of treatment patterns. The very high LLT usage (97 %) suggests the cohort reflects prevalent rather than newly diagnosed cases, and the low ASCVD prevalence (8.6 %) raises concerns about case selection. Defining FH phenotype based on LDL-C ≥ 240 mg/dL (≥ 6.2 mmol/L) without genetic or clinical confirmation may have captured individuals with polygenic or secondary hyperlipidemia. The predominance of women (72.7 %) likely reflects differential healthcare engagement rather than biological difference. Still, these are common constraints in EHR-based research.

A key methodological concern across many FH studies is Berkson bias [17]—a form of selection bias occurring when study populations are disproportionately drawn from individuals already accessing healthcare. This can distort observed prevalence, ASCVD risk, and treatment intensity, as hospital-based or specialist cohorts often include patients with more advanced or atypical disease. To mitigate this, future FH registries should incorporate population-based data from primary care, laboratories, or national health systems, enabling more representative and generalizable findings for clinical and public health planning.

4. What's next? Strengthening early FH detection in primary care

Timely identification of FH in primary care is essential to prevent

lifelong exposure to elevated LDL-C and reduce ASCVD risk. To advance early detection, several strategic actions are needed:

1. **Integration & validation of EHR-based algorithms** using standardized LDL-C thresholds against genetic testing to improve diagnostic accuracy and enable cascade screening.
2. **Implementation studies** to evaluate the impact of EHR alerts and clinical workflows on feasibility, acceptability, and treatment outcomes in real-world practice.
3. **Greater insight into patient- and provider-level barriers**, including treatment adherence, lifestyle factors, and therapeutic inertia.
4. **Sex- and age-stratified analyses** to guide personalized treatment strategies across the lifespan.
5. **Broader application of digital case-finding tools** across diverse regions and healthcare systems to ensure scalability, equity, and global relevance.

5. Conclusion

Gijón-Conde et al. present compelling evidence that FH phenotype is prevalent yet remains largely unrecognized and undertreated in primary care. These findings highlight the burden of FH in this setting and reinforce the need for improved detection and management strategies. The study supports the expansion of algorithmic EHR-based screening and emphasizes the pivotal role of primary care in early FH identification and cardiovascular risk prevention.

To close these gaps, system-level initiatives, professional training, and improved coordination between primary and specialist care are urgently needed. EHRs offer a promising tool for earlier detection and cascade screening, but further studies are necessary to compare the effectiveness, accuracy, and timeliness of different case-finding approaches in routine practice.

There is clear momentum—but still a long way to go—to optimize FH recognition and management where it matters most: at the frontlines of care.

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