



Anxiety, depression, and health-related quality of life in heterozygous familial hypercholesterolemia: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:

Familial hypercholesterolemia
Anxiety
Depression
Quality of life
Health-related quality of life
Systematic review
Meta-analysis

ABSTRACT

Background: Heterozygous familial hypercholesterolemia (FH) is a common genetic disease predisposing affected individuals to a high risk of cardiovascular disease. Yet, considerable uncertainty exists regarding its impact on psychosocial wellbeing.

Objectives: We performed a systematic review and meta-analysis of the association between FH and symptoms of anxiety and depression, and health-related quality of life (HRQL).

Methods: We searched MEDLINE, EMBASE, Global Health, the Cochrane Library, PsycINFO, and PubMed for peer-reviewed literature published in English between January 1, 1990 and January 1, 2018. Quantitative and qualitative studies were eligible if they included patients with confirmed FH and evaluated its association with symptoms of anxiety or depression, or HRQL. We performed a narrative synthesis of studies, including thematic analysis of qualitative studies, and where data permitted, random-effects meta-analysis reporting standardized mean differences (SMD) and 95% confidence intervals.

Results: We found 10 eligible studies measuring HRQL, depression and anxiety. Random-effects meta-analysis of 4 ($n = 4293$) and 5 studies ($n = 5098$), respectively, showed that patients with FH had slightly lower symptoms of anxiety (SMD: -0.29 [95% CI: $-0.53, -0.04$]) and mental HRQL (SMD: -0.10 [95% CI: $-0.20, -0.00$]) relative to general population controls. No significant differences existed in depressive symptoms (SMD: 0.04 [95% CI: $-0.12, 0.19$]) or physical HRQL scores (SMD: 0.02 [95% CI: $-0.09, 0.12$]).

Conclusions: Our systematic review suggests that patients with FH may report small but measurable differences in anxiety symptoms and mental HRQL.

1. Background

Heterozygous familial hypercholesterolemia (FH) has been recently recognized as one of the world's commonest inherited diseases, affecting nearly 1 in 250 individuals [1]. Through defects in the low-density lipoprotein (LDL) receptor pathway, FH predisposes affected individuals to high levels of LDL-cholesterol and concomitant premature atherosclerotic cardiovascular disease (CVD). Natural history studies of FH have demonstrated up to a 100-fold increase in cardiovascular mortality in the young [2] that may be significantly attenuated with adequate treatment [3,4]. This has triggered a strong international

impetus for identifying potentially affected individuals [5] and better understanding the burden of disease [6].

Chronic diseases adversely affect health-related quality of life (HRQL) [7–9] and can predispose individuals to anxiety and depression [10,11]. Over the last decade, increasing evidence suggests that in addition to the suffering borne by patients, anxiety, depression and HRQL also deserve attention because of their relation to increased morbidity and mortality [12–17]. Most studies exploring relationships between genetic conditions and HRQL have few or no subjects with a risk of CVD as high as that of people with FH [18]. Accordingly, conclusions drawn from these samples cannot be reliably extrapolated to

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<https://doi.org/10.1016/j.jpsychores.2018.03.170>

Received 21 December 2017; Received in revised form 24 March 2018; Accepted 24 March 2018
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FH patients. Yet, much of literature examining links between FH and wellbeing outcomes are inconsistent. While some studies have reported better mood and HRQL [19,20], others have not [21–24]. These inconsistencies may be explained by small sample sizes, heterogeneous populations, or differences in study design and instruments used to measure outcomes of interest [25,26]. To overcome some of these limitations and better understand the potential psychosocial effects of FH, we conducted a systematic review and meta-analysis of the association between FH and anxiety, depression, and HRQL.

2. Objectives

1. In a narrative synthesis, to identify how individuals with FH define quality of life.
2. To identify factors associated with anxiety/depression symptoms and quality of life in the FH population.
3. To quantify relationships between FH and symptoms of depression and anxiety.
4. To quantify relationships between FH and HRQL.

3. Methods

This study was part of a series of systematic reviews using a standardized search strategy examining the disease burden posed by heterozygous FH. This review was registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42016042208) and executed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) consensus statement [27].

3.1. Study Identification & Selection

We searched MEDLINE, EMBASE, Global Health, the Cochrane Library, PsycINFO and Pubmed for published, peer-reviewed literature using keywords related to familial hypercholesterolemia. To maximize the sensitivity of the literature search, terms were not restricted to anxiety- or depression-related terminology. Results were limited to human studies published in English between January 1, 1990 and January 1, 2018 to capture the most recent studies published in the statin-era. We reviewed reference lists of all included articles and relevant literature reviews, systematic reviews and meta-analyses for additional eligible studies. A detailed search strategy is included in the supplement to this manuscript (eTable 1).

Titles, abstracts and full-texts were evaluated in duplicate by two independent reviewers using standardized forms (eTable 2). Disagreements were resolved through discussion to consensus. For inclusion in the systematic review, studies were required to: (1) include participants with confirmed FH and (2) assess and report on its association with symptoms of anxiety or depression, or quality of life. We also reported on studies evaluating the quality of life of unaffected family members of individuals with FH as well as characteristics associated with anxiety, depression or quality of life scores. Studies were excluded if they pooled survey or interview data of individuals with FH with other groups without separation into distinct subgroups for analysis.

In cases where missing data from studies could not be derived directly from the published report or calculated based on the available data, the effect sizes were deemed inestimable and results were described narratively or in tabular format. We did not exclude studies from the analysis on the basis of study design or presenting data in only specific age-groups.

Agreement between reviewers on inclusion was evaluated using a kappa statistic. Strength of agreement as evaluated by the kappa statistic was defined as slight (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80) or almost perfect (0.81–1.00) [28].

3.2. Study quality assessment

We assessed the quality of eligible quantitative studies using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool (<http://www.ephpp.ca/tools.html>). The EPHPP tool has been shown to be acceptable for use in evaluating a variety of study designs including randomized controlled trials, before-and-after studies and case control studies (eTable 3) [29]. Each dimension is rated on a three-point scale - strong, moderate, and weak - which is used to derive a global rating of study quality. Global study quality is considered to be strong if none of the quality domains is rated as weak, moderate if one domain is rated as weak, and weak if two or more domains are rated as weak.

Qualitative studies were evaluated using the Qualitative Research Checklist derived by the Critical Appraisal Skills Program (CASP) (eTable 4) [30]. This checklist adds up 10 items, each scored as either 1 = yes (criterion met) or 0 = no (criterion not met), to a maximum possible score of 10. We report the ratio of the obtained score to the maximum possible score for each study and ranked studies as weak (< 0.50), moderate (0.50–0.70), strong (≥ 0.80).

3.3. Data extraction

One reviewer independently extracted data regarding study characteristics (e.g., design, population characteristics, and diagnostic measures) from the full-text of included articles. Another reviewer checked the extracted data and any detected discrepancies were resolved. We did not attempt to contact authors of studies with missing or incomplete data nor did we exclude any such studies from our synthesis. Results described solely in graphical format were extracted using open source software Plot Digitizer (<http://plotdigitizer.sourceforge.net>). Recent investigations demonstrate the ability of software to abstract data with high speed, accuracy, and agreement between raters [31].

3.4. Data synthesis

3.4.1. Qualitative synthesis

We first conducted a thematic analysis of all included studies during data extraction to identify and cluster self-reported impacts of FH on participants' health and psychosocial functioning. In qualitative data synthesis, thematic analysis is useful for identifying major or recurrent themes in eligible studies and permits the summary of their findings under descriptive headings [26,32].

3.4.2. Meta-analysis of quantitative studies

A meta-analysis was undertaken to examine associations between FH and self-reported symptoms of anxiety, depression and HRQL. We calculated a standardized mean difference (SMD) and corresponding 95% confidence intervals (CIs). SMDs are employed as a summary statistic when included studies assess the same outcome but use different metrics [26]. The SMD was determined from mean scores on rating scale summary scores (or sub-components) and their associated standard deviations (SDs) using a DerSimonian and Laird random effects model [33]. Where studies reported only means and ranges or standard errors (SEs), we calculated SDs from published study data. In our results, negative SMDs indicate lower anxiety or depression scores on rating scales in individuals affected by FH, while positive SMDs indicate lower scores in the general population. We multiplied physical and mental component scores of HRQL measures by -1 to maintain the consistency with our anxiety and depression analyses in interpreting the direction of effects sizes. Therefore, negative SMDs indicate higher HRQL in FH-affected groups, while positive SMDs reflect higher HRQL scores in the general population. Conventionally, values of 0.20, 0.50, and 0.80 indicate small, medium, and large effects respectively [34]. For ease of interpretation, we also express odds ratios (ORs)

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