The experiences and needs of supporting individuals of young people who self-harm: A systematic review and thematic synthesis

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Summary
Self-harm in young people is a serious international health concern that impacts on those providing informal support: the supporting individuals of young people. We aimed to highlight the experiences, views, and needs of these supporting individuals of young people. We conducted a systematic review and thematic synthesis: PROSPERO CRD42020168527. MEDLINE, PsycINFO, EMBASE, AMED, CINAHL, ASSIA, and Web of Science were searched from inception to 6 May 2020 with citation tracking of eligible studies done on 1 Oct 2021. Primary outcomes were experiences, perspectives, and needs of parents, carers, or other family members of young people aged 12–25. Searches found 6167 citations, of which 22 papers were included in synthesis. Supporting individuals seek an explanation for and were personally affected by self-harm in young people. It is important that these individuals are themselves supported, especially as they negotiate new identities when handling self-harm in young people, as they attempt to offer support. The GRADE-CERQual confidence in findings is moderate. Recommendations informed by the synthesis findings are made for the future development of interventions. Clinicians and health service providers who manage self-harm in young people should incorporate these identified unmet needs of supporting individuals in a holistic approach to self-harm care. Future research must co-produce and evaluate interventions for supporting individuals.

Introduction
Self-harm is defined as self-injury or self-poisoning irrespective of intent.1 In young people self-harm is an international public health concern: an estimated 26% of young people aged 16–24 have self-harmed, and self-harm can impact young people and their parents, carers, families, and health and social care services.2,3

Young people turn to parents, carers (friends, neighbours, or other informal carers), and other family members for help-seeking and conversely these supporting individuals can encourage young people to seek help; therefore, responses of such supporting individuals are vital for the future help-seeking of young people to reduce repeat self-harm behaviour, emotional distress, and suicide and mortality risk.

Curtis et al., (2018) published a narrative review that included the perspectives of parents and carers of young people who self-harm.4 They found parents’ responses differed depending on how they conceptualised self-harm, but, this review was not a systematic nor expansive representation of the literature,4 meaning that to date, there is no robust systematic review searching several bibliographic databases and synthesising data that explored experiences and needs of supporting individuals (parents, carers, and other family members) of young people who self-harm.4 Bringing together international evidence in this way will allow for a better understanding of the views and needs of supporting individuals of young people who have harmed themselves.
We conducted a systematic review and thematic synthesis of qualitative data to generate a rich understanding about the needs of supporting individuals for young people who self-harm. We aimed to investigate the experiences, perspectives, and needs of supporting individuals of young people (12–25 years old) who have harmed themselves. We anticipate that our findings will inform future evidence-based resources and interventions to enable healthcare professionals (including primary care, emergency department, and mental health professionals) to better support these individuals.

**Methods**

**Protocol**
The protocol was registered on PROSPERO (CRD42020168527). This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Enhancing transparency in reporting the synthesis of qualitative research guidance (ENTREQ) (supplementary Fig. 2).5,6

**Search strategy and information sources**
Seven electronic databases (MEDLINE, PsycINFO, EMBASE, AMED, CINAHL, ASSIA, and Web of Science) were searched from inception to 6 May 2020 using refined and tailored search strategies with the support of an information specialist (NC). Searches combined database subject headings and text word searching in titles, abstracts, and keywords, combining terms for self-harm and parents/family/carers and qualitative studies (see supplementary Fig. 1 for full Ovid MEDLINE search strategy). Self-harm was defined as per National Institute for Health and Care Excellence guidance thus including search terms: ‘attempted suicide’, ‘parasuicide’, and ‘non-suicidal self-injury’.7 We adapted and used the DeJean hybrid qualitative filter because of its high search sensitivity.7

In addition, weekly Web of Science and Google Scholar alerts after 6 May 2020, and citation tracking of included studies on 2 October 2021, allowed for the identification of new relevant evidence. No language or location restrictions were applied.

**Eligibility criteria**
Studies were eligible if they reported data about young people aged 12–25 years who have harmed themselves (including those in professional care) obtained from parents, carers (friends, neighbours, or informal carers), or other family members, including siblings and grandparents. Qualitative and mixed-methods studies reporting qualitative data were included. Table 1 outlines the review eligibility criteria.

| Population | Parents, carers (friends, neighbours, and other informal carers), and other family members (siblings and grandparents) of young people, including those in professional care, 12–25 years old who self-harm |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Intervention/Exposure | Self-harm, non-suicidal self-harm, deliberate self-harm, suicidal attempt, parasuicide |
| Comparator | Nil |
| Outcome | i) Experiences of parents, carers, or families  
ii) Perspectives of parents, carers, or families  
iii) Perceived needs of parents, carers, or families |
| Setting | International primary, secondary, and community care |
| Study design | Qualitative studies  
Mixed-methods studies reporting qualitative data |
| Exclusion criteria | Young people who self-harm  
Formal carers in a professional capacity  
Parents, carers, and family members bereaved by suicide  
Grey literature  
Observational, trial, and cross-sectional studies  
Full text of study not available  
Studies where translation could not be sought |

**Study screening and selection**
Two authors (FM and MIT) independently reviewed all article titles and abstracts, then full-texts in a two-staged approach, against piloted and predefined eligibility criteria. Discrepancies were resolved through discussion. Titles and abstracts not in English were selected for full-text review, and full-text papers in Spanish and French were translated by co-authors to determine eligibility. Reasons for excluding studies after full-text review were documented and are stated in Figure 1. Corresponding authors of five studies were contacted by email for data clarifications: two authors did not reply. Study screening was managed through Endnote X9.8

**Data extraction and quality assessment**
Each included full-text paper underwent data extraction and quality appraisal by two authors (FM and MIT) onto pre-piloted Microsoft Excel spreadsheets. Data were extracted on study title, aim, country and setting, study design, data collection and analysis methods, participant number, age range and gender, language of paper, and
participants’ experiences, perspectives, and needs. All text reported within ‘results’ or ‘findings’ of manuscripts (including author text and participant quotations) were eligible for extraction. The terms ‘experiences’ and ‘perspectives’ were predefined (Oxford English Dictionary) to support consistency in data extraction:

- **Experience**: an event or occurrence which leaves an impression on someone.
- **Perspective**: a particular attitude towards or way of regarding something; a point of view.

Quality assessment of each paper was completed alongside data extraction using the Critical Appraisal Skills Programme (CASP) checklist for qualitative data. Discrepancies in quality assessment were resolved through discussion. Papers were not excluded based on their quality assessment. The GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative Research [https://www.cerqual.org/]) was used to assess the overall confidence of review findings across four domains: methodological limitations, coherence, adequacy of data, and relevance, and was informed by the quality assessment of papers.

**Synthesis**

A thematic synthesis was conducted to stay close to the results of primary studies while facilitating the production of new findings: it was led by FM, in collaboration with all co-authors, guided by Thomas and Harden’s (2008) three steps:

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6167 records identified through database searches

1348 duplicates removed

4819 titles and abstracts screened (n = 4,819)

4773 records excluded

46 full-text studies assessed for eligibility

27 excluded

9 not self-harm specific
10 did not have specific data on young people aged 12-25
5 no outcome of interest
3 unsuitable study design

3 studies identified through alerts and citation tracking

22 papers (reporting on 17 studies) included in qualitative synthesis
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Figure 1. Study selection.
(1) Inductive coding of text line-by-line according to meaning and content.
(2) Development of descriptive themes.
(3) Generation of analytical themes.

FM imported relevant data verbatim into NVivo 12 and coded each line of data inductively. Data extracts were coded against more than one code. Across two meetings the team discussed initial codes and data across studies to support consistency in the interpretation of data. After searching for similarities and differences within and across papers using constant comparison principles, codes were grouped into descriptive themes.

All co-authors used their professional backgrounds (psychology, patient and public involvement, social science, general practice, evidence synthesis, and health services research) and experiences to ‘go beyond’ the primary data and descriptive themes, to generate analytical themes, which were agreed upon by the team. This resulted in new interpretive constructs that significantly increase our understanding about parents, carers, and families of young people who self-harm. At analysis meetings and throughout the synthesis all authors considered how their backgrounds influenced interpretation of data and understanding of findings.

Patient and public involvement
A patient and public involvement (PPI) ‘self-harm in young people’ group at Keele University consisting of one young person with lived experience of self-harm, a parent of a young person who has self-harmed, and two self-harm third sector workers said there is a lack of resources readily available for parents of young people who self-harm, and this informed this study’s conception. A co-author is a parent of a young person who has lived experience of self-harm and contributed to the interpretation of data, generation of themes, and writing of manuscript.

Role of the funding source
This review was supported by the National Institute for Health Research School for Primary Care Research. The funder was not involved in this review’s design, data collection, data analysis, data interpretation, the writing of the manuscript, or in the decision to submit for publication. The views expressed in this article are those of the authors and not necessarily those of the NHS, NIHR, NICE, or the Department of Health and Social Care. All authors had full access to all data in the study and had final responsibility for decision to submit for publication.

Results
The searches yielded 6167 unique records of which 1348 were removed as duplicates. The titles and abstracts of 4819 records were screened and subsequently 46 full-text studies were assessed for eligibility, of which 27 were excluded. Weekly alerts and citation tracking of eligible studies identified three further eligible studies. Therefore, a total of 22 papers reporting on 17 studies published between 2002 and 2021 were included in the qualitative synthesis (Figure 1).

Study characteristics
Studies were conducted in Ghana (n = 1), Denmark (n = 1), France (n = 1), Canada (n = 1), Portugal (n = 1), China (n = 1), USA (n = 1), Sweden (n = 1), Finland (n = 1), Hong Kong (n = 1), Australia (n = 2), and the UK (n = 5); and across a range of settings: specialist paediatric facility (n = 2), hospital (n = 6), and community (n = 9). There was one mixed-methods, one multi-method, and 15 qualitative studies that used semi-structured interviews (n = 10); focus groups (n = 2); unstructured interviews (n = 1); narrative interviews (n = 1); and in-depth interviews (n = 1). There were four linked UK papers, two Finnish, and two from Hong Kong that used the same study sample.

Sample sizes ranged from 3 to 38 with a mean of 15 (SD 12), and ncluded friends (n = 11), family members (n = 9) (sisters n = 3, brothers n = 1, husband n = 1, aunt = 1, grandmother n = 1, male family member/relative n = 2), and parents (n = 233). The age range of participants across studies was 13–62 years and the male to female ratio was 47:200.

Quality assessment and confidence in findings
The characteristics and quality assessment of included papers are stated in Table 2 and supplementary Table 1. The GRADE-CERQual assessment of confidence of review findings is presented in supplementary Table 2.

Final analytical themes
Line by line inductive coding generated 259 codes and 949 data extracts. These informed the identification of 27 descriptive themes: defined in supplementary Table 3. The descriptive themes supported the generation of five analytical themes presented below (illustrated by a thematic map in supplementary Figure 3) which informed seven recommendations (Table 3) for the development of future interventions for supporting individuals:

1 Seeking an explanation

This theme captures parents’, friends’, and other family members’ wish to understand why self-harm happened, and their thoughts on why it happened:
“well self-harm I thought it was like, obviously it is something that can kill you, erm, but like there’s I just thought like, why is it in the world, like why does it have to be here, why do people do this...” (friend)22

“for the majority of the parents, the suicide attempt was the culmination of a prolonged period, often several years, where their child had suffered from psychological

Table 2: Characteristics of included studies.

| Author and Year | Country | Setting | Design and data collection method | Number of participants | Participant age range | Male: female ratio |
|-----------------|---------|---------|-----------------------------------|------------------------|----------------------|-------------------|
| Asare-Doku W et al., 201913 | Ghana | Psychiatric department of teaching hospital | Qualitative: semi-structured interviews | 10 | 25–62 | 5:5 |
| Balcombe L et al., 201114 | UK | Paediatric ward of hospital | Qualitative: semi-structured interviews | 4 | | 2:2 |
| Buus N et al., 201315 | Denmark | Community via third-sector organisation | Qualitative: focus groups | 13 | | 5:8 |
| Daly P, 200516 | Canada | Paediatric health facility | Qualitative: unstructured interviews | 6 | 32–45 | 0:6 |
| De Miranda Trinco ME et al., 201717 | Portugal | Paediatric hospital | Qualitative: semi-structured interviews | 38 | | 4:34 |
| Ferrey AE et al., 201618 | UK | Community | Qualitative: semi-structured interviews | 37 | | 5:32 |
| Fu et al., 202019 | China | In-patient child psychiatry ward, hospital | Qualitative: semi-structured interviews | 20 | | 4:16 |
| Hall S & Meza Y, 202120 | UK | Community | Qualitative: semi-structured interviews | 8 | 13–18 | 0:8 |
| Humensky JL et al., 201721 | USA | Community outpatient clinic | Qualitative: focus groups | 8 | | 0:8 |
| Kelada L et al., 201622 | Australia | Community Mult-methods study: questionnaire and semi-structured interviews | 38 | | 5:33 |
| Krysinska et al., 202023 | Australia | Community | Qualitative: semi-structured interviews | 19 | | 3:16 |
| Lindgren et al., 201024 | Sweden | Community outpatient | Qualitative: narrative interviews | 6 | 44–55 | 1:5 |
| Oldershaw et al., 200825 | UK | Child and Adolescent Mental Health Service | Qualitative: semi-structured interviews | 12 | | 2:10 |
| Raphael et al., 200626 | UK | Hospital emergency departments | Mixed-methods: autobiographical accounts and unstructured interviews | 9 | | 4:5 |
| Rissanen et al., 200827 | Finland | Community | Qualitative: in-depth interviews | 4 | | 1:3 |
| Rissanen et al., 200928 | | | | | | |
| Spiers S et al., 201929 | France | Adolescent Mental Health Service | Qualitative: semi-structured interviews | 15 | | 6:9 |
| Yip K et al., 200230 | Hong Kong | Community | Qualitative: semi-structured interviews | 6 | | |
| Yip K et al., 200331 | | | | | | |
problems and exhibited highly disturbed behaviour, such as self-harm or eating disorders.” (Buus et al.)

Some family members saw young people self-harming as an attention-seeking device:

“his sister disagreed, saying that one reason for his suicide attempt was a search for attention...” (sister).

Conversely, more sympathetic perspectives were expressed about young people being “mistreated by others because of their self-mutilation” (Rissanen et al.).

It was noted that young people engaging in such behaviour have poor self-esteem, with these individuals described as conscientious, kind and caring at home and with their family.

2 Impact of self-harm

This theme encapsulates the effect of self-harm on participants’ lives, wellbeing, and their family, and the necessity of self-care. Participants faced tensions when attempting to support young people versus protecting themselves from mental illness and financial uncertainty because of the support offered.

Self-harm in young people affected all participants who described sleeplessness, depression, and anxiety states:

“I was really upset, couldn’t sleep. I had three months off work and was put on antidepressants, which I take to this day and will never stop taking because they keep me sane” (mother).

Participants developed states of hypervigilance and anxiety about the safety of their young person, fearing repeat self-harm and suicide.

Psychological distress, suicidal thoughts and self-harm were also described by participants who struggled emotionally processing self-harm:

“Emotionally, I’m so tired and I want it to stop and, whilst I would never commit suicide, the thoughts are there at times, you know. I have actually pre-planned what I would do and how I’d do it.” (parent)

“In response to this, participants described how self-care was important in addressing the impact of self-harm, and in supporting one’s family.

Different approaches to parenting could lead to parental conflict, and parents described how parenting approaches changed because of self-harm. As a consequence, self-harm could disrupt relationships participants had with their partners: “...put my marriage under a colossal amount of strain” (mother).

Some parents chose to give their children materialistic compensation such as money or gifts in response to self-harm, and others found it difficult to set boundaries and maintain normal discipline at home due to fear of precipitating a self-harm episode.

In some cases, parents felt that trust had been eroded over time and emotions of betrayal set in, culminating in a palpable distance, and ultimately loss of trust in the relationship between parent and young person.

Participants described how self-harm negatively affected siblings who felt they received less attention at home; in some cases, siblings removed themselves from the family:

3 Importance of being supported

Participants described mixed responses from healthcare professionals in terms of the young person’s self-harm. They reflected on how experiences
of initial care can impact on future help-seeking for the young person. For instance, a mother praised the crisis team who saw her daughter daily:

“I can hand on heart say, that team turned our lives around. They visited my daughter every day for a month but also it was all so joined up... They were incredible people. They would come at whatever time was suitable to us. They would come in the morning. They would come in the evening. Sometimes, they came twice a day” (mother).32

The importance of how healthcare professionals respond to self-harm in young people is highlighted by the following data extract about this young woman’s experience visiting her GP and the impact it had on future help-seeking:

“Although initially Mrs E’s daughter had been willing to see the GP to discuss her self-harm, after his negative response, she tried to deny its existence. Consequently, parent and child began to sidestep the issue once more and it was not discussed again until problems deteriorated several months later.”(Oldershaw et al.)27

Parents were hopeful when they felt valued, listened to, and included in care, as if they were part of the solution and part of the team.26,32 Parents found negotiating the balance between detachment and enmeshment with young people within the wider family challenging.25 A mother described the difficulty of treading a fine line between being a team player in the child’s care, and becoming a manager:

“I have found it very hard trying to stay calm and being positive while my daughter suffered self-harm. I also worry that paying close attention on her makes her feel less independent” (mother).24

4 Negotiating new identities

This theme highlights how self-harm ruptured participants’ sense of identity, in turn influencing their relationships, and how they attempted to manage new emerging identities.

Some parents highlighted a tension between wanting to be a parent, and having expectations of healthcare services:

“I was her therapist instead of just being her mother. To get rid of the anxiety we would talk for hours; she should have had that help from the care providers instead” (mother).26

Other parents felt guilty because of self-harm as they thought they had failed as parents; this led to feelings of self-blame where they questioned their competence as parents and challenged their perception of the relationship with their child.15,25,28. Many parents described shock and devastation: “D. felt ‘absolutely devastated’ and ‘couldn’t believe that this could be happening, not to my daughter’” (mother) and “I was ‘horrified’, ‘shocked’, ‘stunned’, and ‘speechless’” (parent).10,19,24,25,27 Feelings of shock, guilt, and grief led to thoughts of helplessness and hopelessness16,17,25:

“Not having seen this, not having been able to accompany him in his anxieties... For me this is a huge failure, obviously. With a feeling of helplessness and lack of solution to accompany him in these difficult phases” (father).11

This father’s statement not only highlights the consequence of self-harm on self-identity but also the emotion of helplessness, and outlines how participants felt powerless with no resources or guidance for them to use with the young person. Participants reflected on a loss of hope for self-harm ending and a return to their previous identities16:

“This is very difficult; I sometimes lose hope in the future... I’m terrified of the future” (parent).17

Parents explained how they felt the self-harm was stigmatised by healthcare professionals and services.17,26 The shame participants experienced resulted in them feeling invisible to others, identifying themselves as a lone player rather than part of a team, and subsequently they became isolated over concerns of the self-harm being discovered.6,26

Some parents described how self-harm resulted in positive shared changes in their relationship with the young person such as spending more time together and doing joint activities: “we have become much closer and learned to discuss” (parent).26,24,30,33 For friends, self-harm both pushed the friendship apart but could result in a greater connection.31 Friends described how they struggled with deciding whether to maintain trust and confidentiality, or to breach it to seek help and gain more support for the young person.31

5 Trying to manage self-harm

This theme incorporates the emphasised need for guidance on how to support and talk to young people; participants actively seeking help for young people; and their perceptions on the role of therapies, peer-support, and schools. The wish for more information on how to care and what to do next for young people is closely related to participants’ understanding of self-harm in theme one; if self-harm is well understood, it may lead to participants providing more effective support.
Most parents said they would value accessible information on self-harm to help them understand, offer appropriate support, and inform decision making: "Inform yourself from absolutely every source you can find. From other parents, from books, from the internet, from research papers, so that...you know what you’re dealing with" (parent).

This included information on how to behave as parents and how to tell others; parents did not want to feel abandoned and wanted to be able to lean on professional advice when needed. Sometimes, wider family members such as grandparents and siblings were committed to support the family, and read books to understand self-harm, which parents thought brought improvement with regular therapy:

Parents described exerting control over the self-harm by removing access to means, and others acted as a ‘negotiator’ amongst healthcare staff and services:

“She waited for the first appointment without any care for two months at home. They [health care staff on the ward] just gave me a list of names of private therapists and said that I should call them - I called everyone and nobody could care for my daughter because they had no time” (parent).

Parents described different responses to medication and psychological therapy for self-harm. Some found medication and the optimisation of dosages helpful in stabilising mood and reducing stress for young people; others felt medication resulted in side effects (such as insomnia, hair loss, and cognitive impairment) and exacerbated self-harm: “the medication had a lot to do with her behaviours at that particular [self-harm] episode” (mother). Parents described some psychologists as unempathetic and reflected on a perceived lack of professional advice when needed. Sometimes, wider family members such as grandparents and siblings were committed to support the family, and read books to understand self-harm, which parents thought brought improvement with regular therapy:

“Once I knew that C (child) had cut...I immediately told the social worker at school. I thought she could help me deal with my child” (mother).

Discussion

This systematic review, the first to our knowledge to focus solely on parents, friends, and families, identified that these supporting individuals sought to understand self-harm in young people, and highlighted the substantial impact self-harm had on individuals’ mental health and approaches to parenting. The importance of parents and families being supported by healthcare professionals and services is a key finding because these experiences can influence future help-seeking and therefore potentially impact on future care received. Parents and friends described how self-harm affected their self-identity, influenced by healthcare experiences, and that this strengthened or weakened relationships. A key theme generated was on parents and families attempting to manage self-harm through seeking help, leaning on therapies, peer support and schools. It illustrated an unmet need for accessible information to assist them in their role as supporting individuals. Recommendations for the development of future interventions for supporting individuals generated from this review are listed in Table 3.

A systematic review of qualitative data exploring suicidal behaviour in young people and caregivers through a family system lens cited a lack of information on how to get help for suicidal behaviour: this corresponds to the identified unmet need of specific self-harm guidance for supporting individuals in this review. A meta-ethnography of relatives’ experiences providing care for individuals with suicidal behaviour found that peer-support was important in easing relatives’ distress; similarly, our review found that the support of those with lived-experience has a key role in helping individuals manage self-harm in young people specifically. Finally, a review on the effectiveness of psychosocial interventions for informal support persons of people who self-harmed only found four interventions that included informal carers, and all were in young people. This is important for the development of future interventions because we found parents, in particular, wanting to be involved and included in the young person’s care.
The strengths of this review include dual independent screening and selection, data-extraction, and quality appraisal of results from seven databases adhering to PRISMA and ENTREQ checklists, and the inclusion of studies from a range of different healthcare settings. Thematic synthesis was conducted by a multidisciplinary team with professional backgrounds in self-harm, psychology, general practice, social science, evidence synthesis, applied health research, and with PPI, increasing the trustworthiness and credibility of findings. We feel the involvement of patients and public into the development and delivery of this systematic review resulted in meaningful findings and recommendations that can lead to benefit for supporting individuals, young people, clinicians, and health services. The GRADE-CERQual assessment found moderate confidence in findings and this can support the adoption and implementation of these findings into practice and policy.

Limitations of this review include that most of the sample were female, and parents, which restricts the applicability of findings to males and wider family members and friends. Only two studies were conducted in lower- and middle-income countries: Ghana and China, both with variable access to universal health coverage, and this hinders the transferability of findings to these contexts. Only four studies stated the ages of participants which highlights underreporting of the sociodemographic characteristics of study samples. We excluded grey literature so relevant reports from charities or health services may have been missed.

This review addresses an important evidence gap, identifying what is needed to support parents, friends, and families as supporting individuals of young people who self-harm. Self-harm in young people is a serious public health concern. Understanding the needs of supporting individuals allows health services to tailor care towards them in a holistic approach to self-harm care. Healthcare professionals, services, and systems must recognise that these individuals have unique needs and address these through our review-informed recommendations. It is crucial for health policy to provide resources and funding to facilitate the implementation and evaluation of these recommendations. Future research needs to focus on the development and testing of interventions informed by our evidence informed recommendations, in co-production with young people, clinicians, and supporting individuals, to ease the distress and impact of self-harm, and enable these individuals to better support young people.

Contributors
FM, MIT, LD, ST, ET, and CCG contributed to study conception and design, and protocol writing. NC supported the design of the search strategies and identification of eligible studies. FM and MIT undertook independent study screening and selection, data extraction, and quality assessment. MIT and LD translated eligible studies into English. All authors analysed data and contributed to data interpretation. FM wrote the first draft of the manuscript. All authors contributed to critical revision of the manuscript.

Data sharing
Data are available on reasonable request to the corresponding author.

Declaration of interests
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Supplementary materials
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