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Preconception risk assessment for thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease (Review)

Hussein N, Henneman L, Kai J, Qureshi N

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TABLE OF CONTENTS

[Intervention Review]

Preconception risk assessment for thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease

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ABSTRACT

Background

Globally, about 6% of children are born with a serious birth defect of genetic or partially genetic origin. Carrier screening or testing is one way to identify couples at increased risk of having a child with an autosomal recessive condition. The most common autosomal recessive conditions are thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease, with higher carrier rates in high-risk populations of specific ancestral backgrounds. Identifying and counselling couples at genetic risk of the conditions before pregnancy enables them to make fully informed reproductive decisions, with some of these choices not being available if testing is only offered in an antenatal setting. This is an update of a previously published review.

Objectives

To assess the effectiveness of systematic preconception genetic risk assessment to enable autonomous reproductive choice and to improve reproductive outcomes in women and their partners who are both identified as carriers of thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease in healthcare settings when compared to usual care.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Trials Registers. Date of latest search of the registers: 04 August 2021.

In addition, we searched for all relevant trials from 1970 (or the date at which the database was first available if after 1970) to date using electronic databases (MEDLINE, Embase, CINAHL, PsycINFO), clinical trial databases (National Institutes of Health, Clinical Trials Search portal of the World Health Organization, metaRegister of controlled clinical trials), and hand searching of key journals and conference abstract books from 1998 to date (*European Journal of Human Genetics, Genetics in Medicine, Journal of Community Genetics*). We also searched the reference lists of relevant articles, reviews and guidelines and also contacted subject experts in the field to request any unpublished or other published trials. Date of latest search of all these sources: 25 June 2021.

Selection criteria

Any randomised controlled trials (RCTs) or quasi-RCTs (published or unpublished) comparing reproductive outcomes of systematic preconception genetic risk assessment for thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease when compared to usual care.

Data collection and analysis

We identified 37 papers, describing 22 unique trials which were potentially eligible for inclusion in the review. However, after assessment, we found no RCTs of preconception genetic risk assessment for thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease.

Main results

No RCTs of preconception genetic risk assessment for thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease are included. A trial identified earlier has published its results and has subsequently been listed as excluded in this review.

Authors' conclusions

As there are no RCTs of preconception genetic risk assessment for thalassaemia, sickle cell disease, cystic fibrosis, or Tay-Sachs disease included in either the earlier or current versions of this review, we recommend considering potential non-RCTs studies (for example prospective cohorts or before-and-after studies) for future reviews. While RCTs are desirable to inform evidence-based practice and robust recommendations, the ethical, legal and social implications associated with using this trial design to evaluate the implementation of preconception genetic risk assessment involving carrier testing and reproductive autonomy must also be considered. In addition, rather than focusing on single gene-by-gene carrier testing for specific autosomal-recessive conditions as the intervention being evaluated, preconception expanded genetic screening should also be included in future searches as this has received much attention in recent years as a more pragmatic strategy.

The research evidence for current international policy recommendations is limited to non-randomised studies.

PLAIN LANGUAGE SUMMARY

Identifying carrier status for thalassaemia, sickle cell disease, cystic fibrosis, or Tay-Sachs disease in non-pregnant women and their partners

Review question

We looked for evidence to show whether identifying people who are carriers for thalassaemia, sickle cell disease, cystic fibrosis, or Tay-Sachs disease, before pregnancy leads to improving reproductive choice and pregnancy outcomes.

Background

Across the world, about 6% of children are born with a birth defect of genetic or partially genetic origin. Many of these conditions can be passed down from parent to child. There are tests to identify the genetic risk of the most common genetic conditions (thalassaemia, sickle cell disease, cystic fibrosis, or Tay-Sachs disease) before pregnancy. In these conditions, called autosomal recessive conditions, the parents of affected children are 'carriers' of the condition, which means they do not usually have symptoms. All 'carrier' couples will have a 25% chance of having an affected child. Risk assessment for these genetic conditions before getting pregnant would benefit potential parents who may be carriers. This information would give the at-risk couple the opportunity to make fully informed decisions about family planning. However, genetic risk assessment before pregnancy may potentially have a negative psychological impact. This is an updated version of the original review.

Search date

We last looked for evidence on 04 August 2021.

Study characteristics

We did not find any trials that we could include in this review. In an earlier version of this review, we had already found the protocol for a trial that has now published its results, but we have excluded the trial in this version of the review because it did not look at the right topic after all.

Key results

Although no trials were identified in which people taking part would have equal chances of being in either group, there are several studies which are not so strictly designed which support current policy recommendations for genetic risk assessment prior to pregnancy in routine clinical practice. We recommend considering potential observational studies in future reviews as well as looking at 'expanded carrier screening' before pregnancy and not just screening for one condition. Any future trials need to consider legal, ethical and cultural barriers to implementing genetic risk assessment before pregnancy.

BACKGROUND

A glossary of terms is available as an appendix (Appendix 1).

Description of the condition

Genetic medicine is expanding into almost every aspect of health care; reproductive risk assessment during the preconception period is a prime example. Identifying genetic risks before pregnancy or conception might produce significant benefits, such as providing information about the risk of having children with genetic conditions and thus giving couples or prospective parents the opportunity to make more informed reproductive decisions. It has been estimated that a couple has a baseline risk of 2% to 3% of having a child with a congenital or genetic disorder (Teeuw 2010). The probability of having an affected child increases when there is a family history of genetic disorders (Shapira 2006; Teeuw 2010). Globally, about 6% of children are born with a serious birth defect of genetic or partially genetic origin (March of Dimes 2006) with over 1800 genes linked to recessively inherited disorders (Antonarakis 2019).

Preconception risk assessment for autosomal recessive or X-linked recessive genetic disorders would benefit couples who may be carriers. The most common examples of these autosomal recessive disorders are thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease. In these disorders, such carriers are usually asymptomatic; however, their child will be affected if he or she inherits the affected genes from both parents. All carrier couples have a 25% chance of having an affected child. These conditions have a high morbidity risk, are potentially life-threatening and have a significant psychological impact not only on the affected child but also on their families or care givers. These diseases are also more prevalent in individuals of particular ethnic backgrounds (WHO 2000). X-linked recessive genetic disorders include haemophilia A and B, and Duchenne muscular dystrophy. In these disorders, if the mother is a carrier, she has a 25% chance of having a son with the condition in each pregnancy (Haque 2016).

In some countries, the need for medical care for children with these diseases, as well as psychological interventions to offer behavioural and emotional support, imposes a potentially high economic and public health burden (Cornel 2021). In view of the magnitude of these conditions and their implications for children and their families, there have been considerable efforts to identify the genetic reproductive risk for the four specified conditions and offer counselling and support to potential parents before the birth of an affected child. Women and couples at increased genetic risk, as well as healthcare professionals, have recognised the importance of preconception assessment to increase reproductive autonomy (Boulton 1996; Henneman 2001; Holtkamp 2017; Janssens 2014; Locock 2008; Massie 2014; Mennie 1998; Poppelaars 2004; Watson 1999; Wille 2004). To date, the practical experience of reproductive genetic risk assessment for autosomal recessive disorders focuses mainly on the antenatal and newborn periods (Qureshi 2004). Identifying genetic reproductive risk during the antenatal period leaves the couple a short period of time to make difficult or limited choices, such as terminating the pregnancy or continuing with the pregnancy and caring for the affected child (Dormandy 2008). Identifying couples who have confirmed genetic carrier status before conception provides an opportunity for individuals or couples to make fully informed reproductive choices including not having children, PGT using donor gametes, arranging early prenatal diagnosis and antenatal care and also considering adoption of a child (Jones 2002; Wille 2004).

Thalassaemia

According to the March of Dimes Birth Defects Foundation, an estimated 307,900 children are born annually with major haemoglobin disorders, the most common being thalassaemia and sickle cell disease (March of Dimes 2006). Thalassaemia is characterised by the defects or absence of synthesis in one of the two globin chains (α or β) which form the normal adult human haemoglobin molecule; this leads to haemolytic anaemia (Peters 2012). Thalassaemia can be diagnosed by measuring fractions of haemoglobin A and haemoglobin F with high-performance liquid chromatography (HPLC) or electrophoresis. In addition, DNA analysis is required to detect an α or β globin chain mutation (Peters 2012). It is estimated that between two and five per cent of the world's population are carriers and this is more prevalent in the Mediterranean, the Middle East, South and East Asia, and the Pacific, with carrier rates ranging from two per cent to 19 per cent (Modell 2001; March of Dimes 2006). Because of founder effect, carrier rates have also increased in countries that previously had low prevalences (Cousens 2010). Morbidity is related to severe anaemia and an affected child will require lifelong blood transfusions. Multiple blood transfusions may eventually result in iron overload and potentially cause heart failure, infection, hypogonadism, infertility, diabetes mellitus, and hypothyroidism. Affected individuals may die prematurely unless given optimal medical management. In individuals with thalassaemia and their families or caregivers, psychosocial problems have also been reported, for example, stigmatisation, isolation, family adjustment, coping with school and education, and social interaction (Gharaibeh 2009; Ratip 1996; Telfer 2005).

Sickle cell disease

Sickle cell disease is caused by a mutation in the haemoglobin gene (β^S) which individuals inherit from both parents (Weatherall 1997). The WHO estimates that sickle cell disease affects 275,000 conceptions each year globally (Modell 2008; Yusuf 2011). Diagnosis is confirmed using HPLC or electrophoresis with the detection of haemoglobin S and C fraction. It affects mainly individuals of African origin but is also found in Indian and some Mediterranean populations. The reported prevalence of carrier frequency ranges from one to 40 per cent, depending on the population group. The condition causes the red blood cells to have a sickle shape which results in premature haemolysis and can lead to life-threatening acute and chronic vaso-occlusion, including renal and cardiovascular complications. Individuals with this condition are also susceptible to serious septicaemia. Like thalassaemia, individuals and their families are also confronted with psychosocial challenges which include the disruption of school and work, social isolation and loneliness, stigmatisation, bullying, and rejection by peers (Barbarin 1999). Recently, there has been a new development in the treatment of sickle cell disease, somatic genome editing which is currently being studied (Bonham 2019).

Cystic fibrosis

Cystic fibrosis is caused by a mutation in the gene cystic fibrosis transmembrane conductance regulator *(CFTR)*; more than 2000 *CFTR* mutations have now been identified (Bareil 2020). Diagnosis of cystic fibrosis is indicated by phenotypic features (chronic sino-

pulmonary disease, gastrointestinal and nutritional abnormalities, obstructive azoospermia and salt-loss syndromes), a family history of cystic fibrosis or a positive newborn screening test, together with laboratory evidence of a *CFTR* abnormality. Abnormalities in the *CFTR* genes can be identified by elevated sweat chloride concentrations (sweat test), identification of two CFTR mutations, or *in vivo* demonstration of characteristic abnormalities in ion transport across the nasal epithelium. Carriers are confirmed by the identification of a CFTR mutation from the blood or saliva (CDC 2004).

Cystic fibrosis is most common among people of European descent with a carrier frequency of 1 in 25 (Murray 1999). This condition is commonly associated with recurrent pulmonary infections, which potentially lead to bronchiectasis and atelectasis, and also pancreatic exocrine insufficiency. There is currently no cure for the disease, with treatment mainly aimed at improving a person's quality of life. However, in the past years, significant progress has been made, in particular, regarding *CFTR*-directed therapeutics (Patel 2020) The need for emotional and social adjustment is a significant psychosocial consequence for people with cystic fibrosis (Bregnballe 2007; Glasscoe 2008).

Tay-Sachs disease

Tay-Sachs disease is caused by a genetic mutation in the α chains of the hexosaminidase A (Hex A) isozyme in the gangliosides in nerve cells of the brain (Bach 2001). The disease is diagnosed by measuring the activity of hexosaminidase A and further identification of a genetic mutation in Hex A (ACOG Committee Opinion 2017). It is most prevalent in the Ashkenazi Jewish populations, with a carrier frequency of around 1 in 30 (ACOG Committee Opinion 2017). The condition leads to a progressive deterioration of mental and physical abilities. Death usually occurs before five years of age. At present, there is no cure or available treatment.

Description of the intervention

Women and their partners can be assessed during the preconception period to identify if they are carriers of one of these four autosomal recessive conditions, which represent the most common autosomal recessive conditions globally. Cystic fibrosis is most common in Northern European populations; sickle cell disease and thalassaemia are most common non-Northern European populations, and Tay-Sachs disease is most common in individuals of Ashkenazi Jewish ancestry. Approaches to improve health outcomes and reproductive choice in couples who carry these genetic conditions should be generalisable to other, but rarer, autosomal recessive conditions. In populations with high carrier rates or significant burden of affected individuals, or both, carrier screening may be offered during preconception to all women in some healthcare settings (ACOG Committee Opinion 2017). More commonly, women and their partners may be assessed on the need for carrier testing. This assessment would be based firstly on a review of the family history for any of the autosomal recessive conditions or their carrier status; and, secondly, on the ethnic origin of the woman and her partner (Dyson 2006). This assessment of ancestry will identify if the individual originates from an ethnic group with a greater probability of being a healthy carrier of any of the four autosomal recessive disorders; for example, those with Ashkenazi Jewish ancestry are more likely to carry Tay-Sachs disease, whilst those of African descent may carry sickle cell trait. The benefits of recording family history as one of the components of preconception health checks have been reported in previous observational community-based studies for a broad range of genetic conditions (Czeizel 2012; Shaw 2020).

Overall, previous interventions have involved genetic carrier testing or screening (with or without educational support and genetic counselling) or both. There is often confusion between the terms genetic carrier testing and screening (Nuffield Council on Bioethics 1993). Genetic carrier testing refers to the testing of individuals to determine the presence or absence of the carrier status (Human Genetics Commission 2011). This testing could, for example, be in the context of a family history of the autosomal recessive condition or relevant ethnicity. On the other hand, genetic carrier screening involves offering or testing the whole population group irrespective of individual risk (Castellani 2010; Human Genetics Commission 2011). Both genetic carrier testing and screening involve the analysis of blood, tissue or bodily fluid samples.

With regards to the actual genetic carrier tests, currently either HPLC or electrophoresis is used to detect haemoglobin variants and to confirm carrier status for thalassaemia and sickle cell disease (NHS SCT Screening Programme 2013). Carrier status for cystic fibrosis is confirmed by analysing the mutations in the gene CFTR, using DNA commonly obtained from white blood cells, mouthwashes and buccal swabs (Murray 1999). Confirmation of Tay-Sachs disease carrier status comprises of molecular analysis to detect genetic mutations in the α chains of the hexosaminidase A (Hex A) isozyme. To improve the detection rate, this should be combined with biochemical tests (ACOG Committee Opinion 2017).

For each condition, as well as confirmed carrier status identified by genetic carrier tests, there are other laboratory investigations that could indicate a probable carrier state. A microcytic or hypochromic blood picture, or both, without anaemia suggests a probable thalassaemia carrier, whilst a probable sickle cell carrier is indicated by a positive sickle solubility test. Elevated sodium chloride levels in sweat can indicate a probable cystic fibrosis carrier state.

At present, there is no formal or standard recommendation that fully addresses preconception genetic risk assessment (NHS SCT Screening Programme 2013). There is variability in how preconception genetic risk assessment is offered across countries. For example, screening for haemoglobinopathies is offered in pre-marital clinics (Cousens 2010; Samavat 2004), whereas, screening for any reproductive genetic disorder may be offered opportunistically in a range of settings such as family planning clinics (Delatycki 2019; Watson 1999). Similarly, in current clinical practice, preconception risk assessment is not offered systematically, but most commonly offered opportunistically, for example when the issue is brought up by the couple or through family history (Heyes 2004).

Preconception expanded carrier screening

In recent years, next-generation sequencing has enabled the screening of hundreds of genetic conditions in one panel simultaneously, including the four conditions described above, as compared to single gene-by-gene carrier screening offered traditionally (ACOG Committee Opinion 2017 (reaffirmed 2020); Grody 2013). Expanded carrier screening allows testing of all individuals regardless of ancestry, thereby potentially reducing the

risk of stigmatisation of specific groups and a more pragmatic approach to preconception carrier screening. The Superior Health Council of Belgium has proposed an expanded carrier screening for autosomal and X-linked recessive conditions to be offered preconceptionally (Superior Health Council Belgium 2017). Although there is no firm or standard recommendation for preconception expanded carrier screening, professional bodies including the European Society of Human Genetics have published recommendations on how to responsibly implement expanded carrier screening (ACOG Committee Opinion 2017 (reaffirmed 2020)). Currently, the Australian Reproductive Genetic Carrier Screening Project ("Mackenzie's Mission") is developing a carrier screening model which involves gene selection for carrier screening panel, evaluation of uptake, reproductive decisions, ethical and psychosocial aspects as well as cost-effectiveness (Delatycki 2019; Kirk 2021).

How the intervention might work

In the specified autosomal recessive disorders (thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease), preconception genetic risk assessment ensures at-risk couples, in which both the women and her partner are carriers of the specified conditions, are aware that they have a one-in-four chance of an affected child prior to pregnancy, enabling them to achieve fully informed reproductive autonomy (Cannon 2019; Christie 2009; Czeizel 2012; Lena-Russo 2002; Massie 2009). This offers the at-risk couples the opportunity to consider the full range of reproductive options (Borry 2011); for instance, couples may choose to have *in vitro* fertilisation (IVF) with pre-implantation genetic testing (PGT), use donor gametes, adopt a child or remain childless (Human Genetics Commission 2011; Jones 2002; Wille 2004). These options are not available to couples who are only made aware of their reproductive genetic risk during the pregnancy. Of equal importance, if couples who have already been informed of their risk, decide to carry on with pregnancy they may consider and be offered prenatal diagnosis earlier in pregnancy. This enables the option of termination in early gestation or can enhance preparation for foetal and maternal well-being throughout pregnancy, preparation following the birth of an infant, and postnatal support. (Wille 2004). If the carrier testing is implemented in the antenatal period, all of these decisions are delayed (Qureshi 2004). With regards to family history assessment, participants have acknowledged that this intervention enables pregnancy planning (Rose 1999) and early identification of couples at reproductive genetic risk (Czeizel 2012).

While the aim of preconception genetic risk assessment is to enable informed reproductive choices, in communities where families are affected by a high burden of disease, prevention of the birth prevalence of disease seemed appropriate (de Wert 2012). At a societal level, preconception carrier state identification has reduced the rate of affected births (Angastiniotis 1998; Cannon 2019; Samavat 2004). Although it is estimated that preconception screening programmes worldwide have caused a small decrease in affected births for haemoglobin disorders from 2.7 per 1000 conceptions to 2.55 per 1000 conceptions over a five-year period from 1998 to 2003, more data and across all common autosomal recessive conditions need to be explored (Modell 2008). Similarly, early observational studies involving genetic carrier screening programmes for Tay-Sachs disease and thalassaemia in Canada and France carried out in high school students were associated with an increased rate of early prenatal diagnosis and termination of affected pregnancies (Lena-Russo 2002; Mitchell 1996; Zeesman 1984). In Cyprus and Iran, the prevalence of thalassaemia has decreased tremendously with the introduction of mandatory pre-marital genetic carrier screening programmes (Alswaidi 2009; Angastiniotis 1998; Samavat 2004). In Hungary, preconception screening has resulted in improved identification of carrier couples and access to genetic counselling services (Czeizel 2012). The introduction of preconception expanded genetic screening allows for the detection of more carriers and carrier couples and potentially maximises opportunities for reproductive autonomy with a much wider array of reproductive risks; however, it has its own ethical, legal and social challenges (van der Hout 2016).

Why it is important to do this review

While a number of observational studies have reported the potential benefits of preconception risk assessment for genetic conditions in general (Czeizel 2012), and specifically for cystic fibrosis (Christie 2009; Massie 2009), haemoglobinopathies (Cao 1996) and Tay-Sachs disease (Mitchell 1996), as with other programmes for genetic testing or screening, this has potential adverse effects. Genetic assessment for reproductive risk has been linked to psychological distress such as anxiety; however, the raised anxiety was a transient phenomenon (Archibald 2011; Bekker 1994). Further, it has been reported that carrier status may be associated with a poor perception of health (Henneman 2001) and may have an impact on the carrier's relationships with their partner (Fanos 1995). Although the occurrence is low, social impacts such as stigmatisation and discrimination have been reported with mandatory carrier screening (Bonham 2010; Kenen 1978; Whitten 1973). Despite these reported adverse effects, there are numerous psychological benefits including the opportunity for informed decision-making and reproductive autonomy in prospective parents (Anido 2005; Archibald 2011; Cannon 2019; Lewis 2011).

With regards to the economic implications, as for other programmes for genetic testing and screening, there is an opportunity cost for redistributing resources from medical care to preconception risk assessment (WHO 1968). Addressing cost-effectiveness in preconception carrier screening can be ethically sensitive (Cornel 2021). Several economic appraisals of haemoglobinopathies screening in the antenatal and neonatal settings have nevertheless indicated that these strategies are cost-effective (Davies 2000; Zeuner 1999). A review of existing screening programmes in Australia has shown that targeted preconception screening in certain ethnic groups demonstrates both clinical and cost-effectiveness (Lew 2014).

At a policy level, preconception genetic risk assessment has been recommended in clinical practice in the Netherlands, the USA and the UK (ACOG Committee Opinion 2009; Health Council of Netherlands 2007; Human Genetics Commission 2011). However, a comprehensive review of the current evidence still needs to be undertaken to directly inform healthcare practice.

This review will explore if robust trial evidence exists on the effect of preconception genetic risk assessment for genetic disorders, particularly before its widespread routine implementation in current healthcare settings. This is an update of a previously published review (Hussein 2015; Hussein 2018).

OBJECTIVES

The purpose of this review is to assess the effectiveness of systematic preconception genetic risk assessment to enable autonomous reproductive choice and to improve reproductive outcomes in women and their partners who are identified as carriers of thalassaemia, sickle cell disease, cystic fibrosis or Tay-Sachs disease in healthcare settings when compared to usual care.

METHODS

Criteria for considering studies for this review

Types of studies

We planned for this review to include all relevant randomised controlled trials (RCTs) and quasi-RCTs.

Types of participants

Women and their partners of reproductive age (aged 16 to 50 years old) who are carriers for thalassaemia, sickle cell disease, cystic fibrosis or Tay-Sachs disease, accessing any healthcare services which include hospitals and community-based healthcare settings. Community-based healthcare settings include family or general practices, community health centres, community health services, community or outpatient clinics and ambulatory care services. Settings outside of healthcare do not directly inform healthcare practice, and thus will be excluded as being outside the scope of this review. If trials contain both eligible and ineligible participants, they will be included if data on eligible participants can be extracted.

Types of interventions

We planned to assess the effects of systematic preconception genetic risk assessment for thalassaemia, sickle cell disease, cystic fibrosis or Tay-Sachs disease, in any healthcare setting. We define systematic preconception genetic risk assessment as a package of risk assessment including one or more of these components:

- family history assessment;
- assessment of ethnicity background;
- genetic carrier testing;
- genetic carrier screening.

Risk assessment can be offered at anytime prior to conception.

We planned to compare systematic preconception genetic risk assessment with standard care. We define standard care as where people receive usual or alternative care in any healthcare setting, that does not involve a specific systematic offer or approach to preconception genetic risk assessment.

Types of outcome measures

The listed outcomes do not form part of the eligibility criteria for the included trials.

Primary outcomes

1. Reproductive outcomes in women and their partners who are carriers of thalassaemia, sickle cell disease, cystic fibrosis or Tay-Sachs disease identified during or after pregnancy
   a. number of infants born with genetic conditions
   b. number of infants born with congenital anomalies
   c. number of infants born with low birth weight
   d. number of infants born prematurely
2. Decisions about future conception and pregnancy in women and their partners who are carriers for thalassaemia, sickle cell disease, cystic fibrosis or Tay-Sachs disease
   a. number of women or couples who would make use of prenatal diagnosis
   b. number of women or couples who would make use of prenatal diagnosis and consider termination of pregnancy if the child is affected
   c. number of women or couples who would consider PGT and IVF
   d. number of women or couples who would conceive using donated gametes
   e. number of women or couples who would consider adoption
   f. number of women or couples who would refrain from having any children
3. Number of women or couples who make an informed choice measured by tools such as the Multidimensional Measure of Informed Choice (MMIC)

Secondary outcomes

1. During pregnancy following intervention
   a. gestational date of prenatal diagnosis in at-risk women
   b. gestational date of prenatal counselling in at-risk women or couples
2. Self-reported measures (short-term change from baseline)
   a. any objective measures of health-related quality of life resulting from preconception genetic risk assessment, using validated tools such as Short Form Health Survey 36 (SF36) and Health Questionnaire EQ-5D
   b. any objective measures of quantifying psychological or social outcomes or both resulting from preconception genetic risk assessment using validated tools such as Spielberger State-Trait Anxiety Inventory (STAI), Perceived Stress Questionnaire (PSQ)
   c. knowledge (any measures of the women's or couples' or both, knowledge of reproductive genetic risk associated with carrier status for thalassaemia, sickle cell disease, cystic fibrosis or Tay-Sachs disease using validated self-reported questionnaire)
   d. satisfaction (any measures of the women's or couples' or both, satisfaction with the intervention using validated self-reported questionnaire)
3. Cost of the intervention (including follow-up visits and tests)

Search methods for identification of studies

We searched for all relevant published and unpublished trials without restrictions on language, year or publication status. If we identify potentially eligible non-English language trials in future searches, we will source a person who can read the language

in order to assess these trials for possible inclusion and data extraction.

Electronic searches

We sought trials from the relevant Cystic Fibrosis and Genetic Disorders Group's Trials Registers using the terms: ((carrier* OR trait OR risk assessment OR Tay-Sachs):kw) AND ((cystic fibrosis OR haemoglobinopathies OR Tay-Sachs):kw). For full details of all searching activities for the registers, please see the relevant section of the Cystic Fibrosis and Genetic Disorders Group's website.

Date of latest search: 04 August 2021.

In addition, we searched all relevant trials from the following databases:

1. Ovid MEDLINE (1970 until 25 June 2021);
2. Ovid Embase ((1974 until 25 June 2021);
3. CINAHL (1970 until 25 June 2021);
4. Ovid PsycINFO (1970 until 25 June 2021).

Date of latest search: 25 June 2021.

The search strategies are available in the appendices (Appendix 2). Start dates for database searches are set to when carrier screening or testing was first available. Based on WHO reports, earliest carrier status assessment was introduced for Tay-Sachs disease and haemoglobinopathies from the early 1970s (Angastiniotis 1995; Kaback 2000). We searched for relevant trials in the databases from 1970 or from when the date of the database was first available if after 1970.

We searched the following clinical trial databases for ongoing and unpublished trials:

- National Institutes of Health database;
- Clinical Trials Search Portal of the World Health Organization;
- Current Controlled Trials in the metaRegister of controlled clinical trials

Date of latest search: 25 June 2021.

Searching other resources

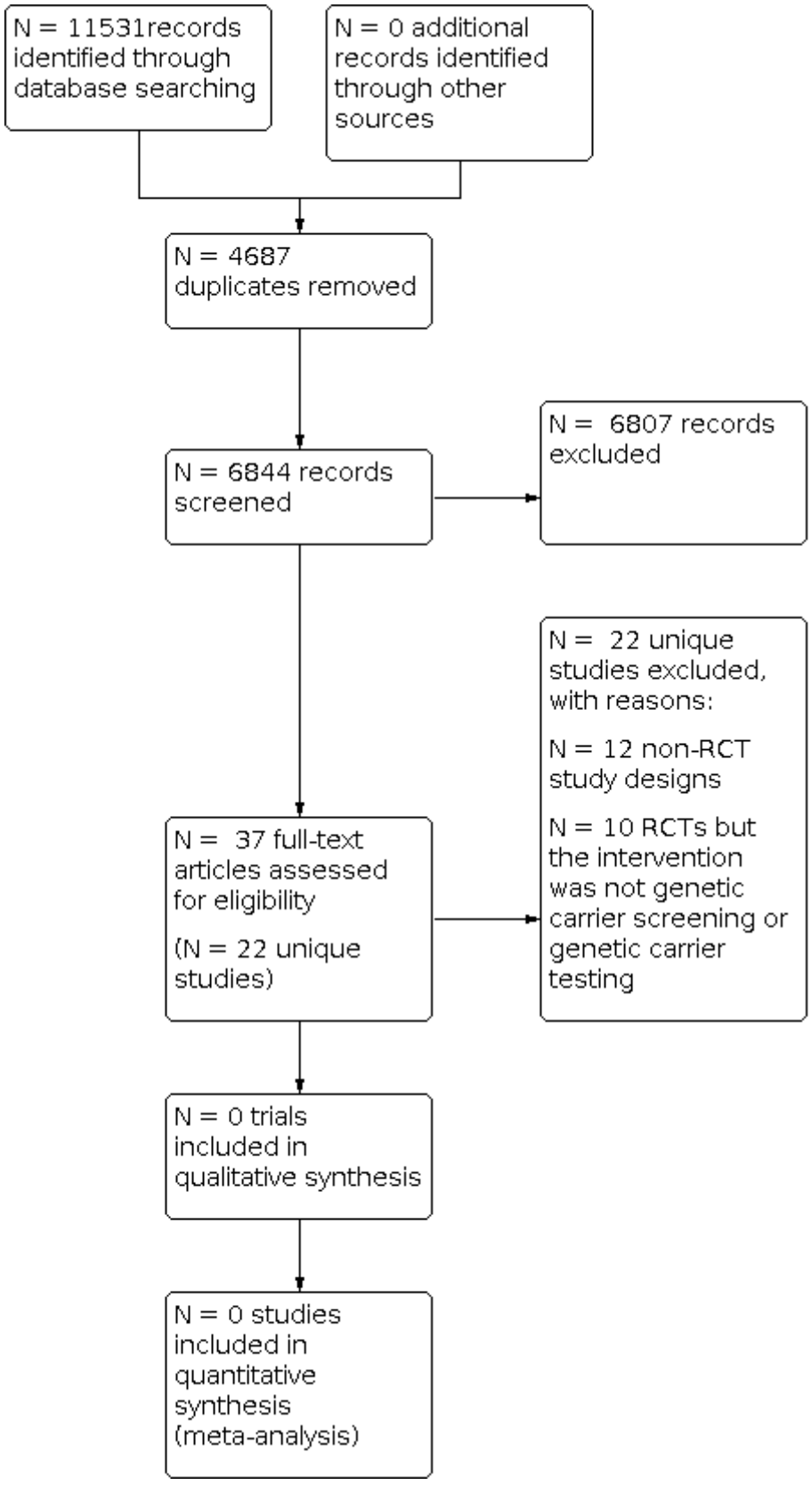
We planned to examine the reference lists of eligible published trials to identify further relevant trials. We handsearched the key journals *European Journal of Human Genetics, Genetics in Medicine* and the *Journal of Community Genetics* from 1998 to June 2021. We complemented the search by contacting subject experts or centres in the field to request any unpublished or other published trials that we may not have identified.

Data collection and analysis

Selection of studies

We saved the results of the searches in the Endnote reference managing software (EndNote X9). Two review authors (one content expert and one methodologist) independently screened the citations and article abstracts of every retrieved record. We would have resolved any disagreements on eligibility by discussion and if doubt remained, we would have acquired the relevant full article(s) for further inspection. Two review authors independently screened all full-text articles of the eligible trials. We aimed to resolve any disagreement by discussion. If required, we would have consulted a third review author. If necessary, we planned to contact the authors of the articles for further information and clarification of trials. We have reported reasons for excluding trials and provided a PRISMA flowchart (Figure 1).

Figure 1. Study flow diagram



We did not identify any trials for inclusion in this version of the review. However, if we identify any trials for future updates of the review, we plan to undertake the following.

Data extraction and management

Two review authors will independently extract data from each included trial using an agreed data extraction form. We will collect data on trial population characteristics (including sample size, participants' ethnic or cultural characteristics, geographic locations), intervention characteristics (including process and duration of intervention) and primary and secondary outcome measures of interest. We plan to report short-term outcomes post intervention up to six months. We plan to report long-term outcomes post intervention from six months up to 12 months, and then annually thereafter.

We will settle any disagreements about the data extracted through discussion by the two review authors, and if necessary by arbitration with a third author. We will enter all the data into the Review Manager software (RevMan 2014).

Assessment of risk of bias in included studies

We will construct a risk of bias table for each trial as outlined in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Two review authors will independently assess and record the following six domains in the risk of bias table:

1. random sequence generation;
2. allocation sequence concealment;
3. blinding of participants, trial personnel, outcome assessors;
4. incomplete outcome data;
5. selective outcome reporting;
6. other sources of bias.

We will judge the methods used in the trials for each domain as having either a low, high or unclear risk of bias. Two review authors will aim to resolve any disagreements in the judgement of the domains through discussion. If no agreement can be reached, then they will consult a third author and aim to resolve the disagreement by consensus.

We will record the information in the 'Risk of bias' tables in Review Manager (RevMan 2014). We aim to resolve any disagreement by consensus or arbitration by a third author. We will use the results of the risk of bias assessment to provide an evaluation of the overall risk of bias of the included trials based on the approach outlined in the chapter 8 (Table 8.7a) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Measures of treatment effect

We will extract all the main results of the included trials as mentioned below. We will contact relevant authors of the original reports for data or any missing relevant information or when clarification is needed. We will settle any disagreements about the data extracted through discussion and if necessary by arbitration by a third author. We will enter all the data into the Review Manager software (RevMan 2014).

Continuous data

For scale-derived data, we will include continuous data from rating scales only if the measuring instrument has been validated. We will include endpoint data and only use change data if the former are not available. For continuous outcomes we will record mean, standard deviation (SD) and number of participants for each group and report effect size using the mean difference (MD) for the same units of measurement or the standardised mean difference (SMD) when different scales are used to evaluate the same outcome, with 95% confidence intervals (CI). The MD measures the absolute difference between the means in two groups, whereas the SMD is the MD relative to variability observed in that trial.

Dichotomous data

We will report dichotomous data using the risk ratio (RR) and the corresponding 95% CIs.

Unit of analysis issues

We anticipate cluster-randomised designs to be used in the included trials; for example, groups of patients of a single doctor or practice. If available, we will extract the direct estimate of the effect (RR with CI) that accounts for a cluster design. We will contact the primary authors of the included trials to obtain the intra-cluster correlation coefficient (ICC) which will describe the relative variability within and between clusters, to adjust for clustering effect (Donner 1980). We will meta-analyse the appropriate analyses of cluster randomised trials using the generic inverse variance method. Alternatively, we will estimate an ICC to describe the relative variability within and between clusters (Donner 1980). An ICC usually derives from the trial or from other sources (ICC from a similar trial in an existing database) (Ukoumunne 1999). If the ICC is derived from other sources, we will report this and conduct a sensitivity analysis. If the trials were analysed as if the randomisation was performed on the individuals rather than the clusters, we will re-calculate the correct analysis if we are able to extract the following information: the number of clusters randomised to each intervention group; the mean size of each cluster; and the outcome data ignoring the cluster design for the total number of individuals.

If we identify more than one intervention group of interest in a trial, we will analyse the effect of the additional intervention group using pair-wise comparisons. If the additional intervention group is irrelevant, we will not reproduce the data.

Dealing with missing data

Whenever possible, we will contact the original investigators and the authors of the included trials to request any missing data. If this is unsuccessful we will deal with missing data as mentioned below.

Overall loss of credibility

We will choose that, if for any particular outcome there is a high risk bias for missing data according to the risk of bias assessment, we will not use these data in the analyses and will present the results in the form of a narrative synthesis.

Continuous data

If SDs are not reported or available, we will first look for statistics that allow the calculation of the SD (for example, the CI and the standard error (SE) of group means, as well as P values and T

values for the differences in means). If this is not possible, we will consider imputing SDs of other included trials. We will examine the consequences of imputations in a sensitivity analysis.

Assessment of heterogeneity

Clinical heterogeneity

We will consider clinical heterogeneity which can result from differences between trials in characteristics of the populations, interventions and outcomes. We will fully discuss the influence of clinical heterogeneity on the observed effects.

Methodological heterogeneity

We will assess for methodological heterogeneity, which can result from differences in characteristics of the trial designs. We will fully discuss the influence of methodological heterogeneity on the observed effects.

Statistical heterogeneity

We plan to examine graphs or summary tables of the trials to investigate the possibility of statistical heterogeneity. We plan to consider the I^2 statistic which estimates the proportion of variability in effect estimates that is due to heterogeneity (Higgins 2002). We will determine the level of heterogeneity by the following reference ranges: low 0% to 40%; moderate 41% to 75%; and high 76% to 100%. We also plan to use the Chi^2 statistic and if the P value is less than 0.10 it will be considered an indication of heterogeneity. If there is a high level of heterogeneity between trials, it may not be appropriate to conduct a meta-analysis, thus we will present results in a qualitative analysis. These trials will be entered into RevMan and presented on a forest plot with their individual effect sizes, but with no combined effect to give an overall picture of evidence (RevMan 2014).

Assessment of reporting biases

If we include and combine more than 10 trials, we will create a funnel plot to investigate the possibility of small trial effects (a tendency for the intervention effects estimated in smaller trials to differ from those estimated in larger trials) (Sterne 2011).

Data synthesis

We will summarise all trials using narrative synthesis methods. This will involve the use of narrative text and tables to summarise data, consider outcomes in the light of differences in trial designs and address potential sources of bias for each of the trials being reviewed. We will group trials according to types of genetic conditions, and then organise them in terms of intervention and outcomes. We will summarise the results of the trials, including the range and size of any reported associations and important trial characteristics. We will also include a detailed commentary on the major methodological problems or biases affecting the trials, together with a description of how these may have affected the individual trial results.

We will use a random-effects model to conduct the meta-analysis due to anticipated differences between trial location and population. If there is substantial variation in results, particularly if there is inconsistency in the direction of effect, we will not perform a meta-analysis.

Subgroup analysis and investigation of heterogeneity

The authors will perform subgroup analyses where sufficient data are available. In the subgroup analyses, the authors will analyse the data in pre-specified subgroups of trials that share characteristics of interest, to see whether the intervention effect remains consistent or whether it varies for particular characteristics of trials. For this review, the authors aim to compare the effects of interventions on outcome measures in the following groups by:

- healthcare setting (primary, secondary, tertiary care or other);
- intensity of the intervention (number or duration of intervention sessions);
- nature of carrier status testing (confirmed genetic carrier status compared to probable carrier status);
- type of condition.

Sensitivity analysis

If there is a spread of bias across the trials, we will provide two estimates of the intervention effect; firstly for all included trials, and secondly only including trials with an overall assessment of a low risk of bias.

Summary of findings and assessment of the certainty of the evidence

For future updates of this review, we will present the main results of the included trials in a summary of findings table for each comparison we report. We will group the trials according to types of genetic conditions, interventions (versus usual care) and outcomes. We will include the following outcomes in each summary of findings table.

- Number of women or couples who refrain from having biological children with their current partner - up to 24 months post intervention
- Number of women or couples undergoing IVF with PGT or using donor gametes - up to 24 months post intervention
- Number of women or couples undergo prenatal diagnosis and consider termination of pregnancy if the child is affected - up to 24 months post intervention
- Number of women or couples who make an informed choice measured by tools such as the MMIC - at 0 month (at intervention)
- Psychological outcomes resulting from preconception genetic risk assessment quantified by validated tools such as STAI, PSQ and health perception questionnaires - at three months post intervention
- Psychological outcomes resulting from preconception genetic risk assessment quantified by validated tools such as STAI, PSQ and health perception questionnaires - at six months post intervention
- Self-reported satisfaction score at 0 month (at intervention)

Overall grading of the evidence related to each of the outcome will use the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach. We will grade the certainty of the evidence as high, moderate, low or very low, based on the five GRADE domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias (Schünemann 2021). We will produce the summary of the findings tables using the GRADEpro software.

RESULTS

Description of studies

Results of the search

Database searching identified 11,531 records. After we screened 6844 unique records, we retrieved 37 full-text articles describing 22 unique trials for further analysis. We found no RCTs that were eligible for inclusion in the review. A flow diagram illustrates the search flow process (Figure 1).

Included studies

No RCTs were found to be eligible for inclusion in the review.

Excluded studies

We excluded a total of 22 trials. We excluded 12 studies due to their non-RCT study designs (Alhamdan 2007; Archibald 2017; Bekker 1993; Childs 1976; Clayton 1996; Hegwer 2006; Henneman 2001; Honnor 2000; Payne 1997; Sallevalt 2021; Tambor 1994; Watson 1991), while 10 RCTs were excluded because the intervention was not preconception genetic carrier testing or genetic carrier screening for any of the four specified genetic conditions (Castellani 2011; Cheuvront 1998; Fan 2018; Fisher 1981; Moudi 2016; Punj 2018; Quigley 2018; Rémus 2020; Temme 2015 Wilkie 2013). One of these 10 RCTs was previously listed as ongoing (protocol by Kauffman from 2017 identified in earlier search); on assessing the published paper containing the full results, we excluded the trial because the intervention was genome sequencing (Punj 2018). The tables summarise the study details and reasons for exclusions (Characteristics of excluded studies).

Risk of bias in included studies

No trials were included in this review.

Allocation

No trials were included in this review.

Blinding

No trials were included in this review.

Incomplete outcome data

No trials were included in this review.

Selective reporting

No trials were included in this review.

Other potential sources of bias

No trials were included in this review.

Effects of interventions

No trials were eligible for inclusion in this review.

DISCUSSION

To date, in many countries, reproductive genetic risk assessment for autosomal recessive disorders has focused on the antenatal period and carrier status that has emerged as an incidental finding in neonatal screening. In the antenatal period, carrier status is identified either through formal screening programmes, or opportunistically during antenatal follow up in women at increased risk based on ancestry. During the antenatal period, if both parents are found to be carriers of the genes (at-risk couples), prenatal diagnostic tests, such amniocentesis, may only be available either late in the first trimester or in the second trimester of pregnancy, which leaves the couple only a short period of time to make limited and difficult choices about termination or continuation of the pregnancy. This limits reproductive choices, with the potential of increased psychological distress in at-risk couples (Modell 1980a; Modell 1980b). The incidental finding of the carrier state during neonatal screening for the specific disorders has highlighted concerns from at-risk couples about the failure to offer this information prior to pregnancy (Locock 2008).

Identifying those couples before pregnancy, who have a confirmed genetic carrier status for thalassaemia, sickle cell disease, cystic fibrosis, or Tay-Sachs disease may provide the opportunity for individuals or couples to make fully informed reproductive choices such as avoiding pregnancy, pre-implantation diagnosis, in vitro fertilisation, arranging early prenatal diagnosis, or consideration of adoption.

Summary of main results

There is currently no evidence from RCTs for the impact of genetic risk assessment for these conditions in non-pregnant women on pregnancy outcomes, informed reproductive choices or psychological adverse effects.

We identified a number of observational studies that were excluded from the review (Alhamdan 2007; Archibald 2017; Bekker 1993; Childs 1976; Clayton 1996; Hegwer 2006; Henneman 2001; Honnor 2000; Payne 1997; Sallevalt 2021; Tambor 1994; Watson 1991). The majority of these observational studies used before and after intervention designs (Bekker 1993; Clayton 1996; Hegwer 2006; Henneman 2001; Honnor 2000; Payne 1997; Tambor 1994; Watson 1991), while four studies utilised cross-sectional designs (Alhamdan 2007; Archibald 2017; Childs 1976; Sallevalt 2021). We also identified 10 RCTs; however, nine of these did not evaluate preconception genetic risk assessment for the four specified genetic conditions (Castellani 2011; Cheuvront 1998; Fan 2018; Fisher 1981; Moudi 2016; Quigley 2018; Rémus 2020; Temme 2015; Wilkie 2013) and one study involved genome sequencing as the intervention (Punj 2018). Only a few studies have assessed reproductive intentions (Cheuvront 1998; Henneman 2001; Watson 1991), whilst no studies have assessed actual reproductive outcomes. Most of the above studies have assessed psychological, attitudes, or knowledge outcomes, but there was some heterogeneity in these outcomes between and within studies. Further, none of the outcome measures for knowledge had used validated instruments. Although study participants recognised the importance of identifying genetic carrier states before pregnancy, different attitudes towards genetic testing were elicited and reproductive intentions varied following positive test results. In the Netherlands, study participants would consider prenatal diagnosis and abortion if an affected foetus is identified (Henneman 2001). In contrast, in a study of cystic fibrosis screening conducted in the state of Tennessee in the USA, reproductive intentions were limited by cultural and socio-political factors, such as insurability, being labelled as 'at risk', a lack of understanding, and religious beliefs about abortion (Clayton 1996). In addition, barriers to implementation include legal discrimination (Lapham 1996) and

religious restrictions on abortion (Fowzan 2001). Previously there were also concerns about fears of stigma (Kenen 1978).

Overall completeness and applicability of evidence

We did not identify any evidence for inclusion in our review.

Quality of the evidence

We did not identify any evidence for inclusion in our review.

Potential biases in the review process

The review authors have attempted to limit the bias in the review process through multiple authors and non-author contributors who independently searched for trials, screened titles and abstracts, selected full-text articles and extracted data. Any disagreements were resolved by group discussion and consensus, and therefore it was unlikely that trials have been incorrectly excluded. Although all clinical trials should be registered, there is always the potential of publication bias. However, attempts have been made to minimise publication bias through searching the grey literature and contacting key experts in the field.

In addition, while not of concern for the current review version, for future updates, rather than focusing on single gene-by-gene carrier testing for specific autosomal-recessive conditions as the intervention under study, preconception expanded genetic screening should also be included in searches as this has replaced the single gene intervention in recent years.

Agreements and disagreements with other studies or reviews

This is the only systematic review looking at preconception genetic risk assessment for thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease and there were no randomised controlled trials eligible for inclusion, and therefore no comparisons could be made to other reviews or studies.

AUTHORS' CONCLUSIONS

Implications for practice

We have not identified any relevant trials up to the 2021 update and this systematic review shows that there is a complete lack of randomised controlled trials (RCTs) in the field of preconception genetic risk assessment for autosomal recessive conditions.

As such, healthcare providers need to assess whether the information provided in published policy recommendations (see below) and non-randomised studies (for example prospective cohorts or before-and-after studies) is relevant to inform their preconception screening practice. While RCTs are theoretically desirable to inform evidence-based practice and robust recommendation, such trials must also consider the ethical, legal and social implications associated with implementation of preconception genetic risk assessment involving carrier testing and reproductive autonomy. Perhaps it is time to rethink whether using RCTs to explore the evidence for reproductive genetic risk assessment is the way to move forward when recommending policy? Furthermore, to consider whether it is ethically acceptable to involve women and men preconceptionally for genetic carrier testing in prospective randomised trials? Healthcare providers have to balance the benefits of increasing reproductive choice against the potential psychological adverse effects from preconception genetic risk assessment, whilst taking into account the legal and socia-cultural context of their healthcare setting and patient population.

Despite the lack of RCT evidence and the research evidence for current policy recommendations being limited to non-randomised studies, a number of international organisations have recommended offering preconception genetic risk assessment routinely at the population level (ACOG Committee Opinion 2009; ACOG Committee Opinion 2017; ACOG Committee Opinion 2017 (reaffirmed 2020); Health Council of Netherlands 2007; Human Genetics Commission 2011; Johnson 2006; March of Dimes 2006). In the USA, the recommendations to improve preconception healthcare were developed through collaborative efforts of the Centres for Disease Control and Prevention (CDC), March of Dimes and the American College of Obstetrics and Gynaecology (ACOG) (ACOG Committee Opinion 2017; Johnson 2006). For instance, the ACOG Committee has recommended that for couples planning pregnancy to identify if either member of the couple are of Eastern European (Ashkenazi) Jewish ancestry or have a family history of relevant recessive genetic diseases (such as Tay-Sachs disease and Cystic Fibrosis), and furthermore that such couples should be offered carrier screening before conception or early in pregnancy (ACOG Committee Opinion 2009; ACOG Committee Opinion 2017).

Similarly, the Health Council of Netherlands has recognised the seriousness of these conditions and high prevalence in local population groups, advocating preconception genetic risk assessment for cystic fibrosis, sickle cell and thalassaemia (Health Council of Netherlands 2007). However, despite local initiatives, large-scale studies have not been implemented in the Netherlands (Delatycki 2019).

The WHO's Regional Office of Eastern Mediterranean recommends preconception genetic risk assessment for sickle cell and thalassaemia ideally before marriage, taking account of the socio-cultural issues in the region, in particular religious reservations towards the termination of pregnancy (Alwan 1997). Since the 1970s, the Cyprus Thalassaemia Control Programme has been at the forefront of premarital genetic screening and this has contributed to a fall in the prevalence of thalassaemia in the country (Angastiniotis 1981). This universal premarital approach to thalassaemia carrier screening has also been adopted by Sardinia, Italy (Cao 1996) and Greece (Loukopoulos 1996).

In line with international policy recommendations, the UK Human Genetics Commission has recognised that since antenatal screening is currently already offered for genetic conditions such as sickle cell disease and thalassaemia, there are no ethical, legal or social issues with regards to the implementation of a preconception screening programme which would provide the advantage of improving reproductive choices (Human Genetics Commission 2011).

In South-East Asia, the Family Planning Association of Hong Kong has recognised the benefits of preconception screening of genetic risk due to the high prevalence of thalassaemia carriers, accounting for up to eight per cent of the local population (Lau 1997).

Implications for research

It has been suggested that the optimum evidence to evaluate the reproductive and psychological outcomes as a result of preconception screening compared to standard practice is a systematic review of RCTs, or a high-quality RCT with a large enough sample size to ensure the control of potential confounding factors (UK National Screening Committee 2003). Such trials address methodological issues that are particularly associated with screening interventions such as ascertainment bias due to non-randomisation, with individuals joining screening programmes tending to have healthier lifestyles and better adherence to interventions (Smith 2003).

Previous observational studies and RCTs on preconception genetic risk assessment for thalassaemia, sickle cell disease, cystic fibrosis, or Tay-Sachs disease have been limited by the duration of follow-up and restricted to the assessment of psychological or knowledge outcomes. Indeed, none of the excluded studies identified in the searches for this review has evaluated reproductive outcomes. This is possibly related to the limited duration of follow-up in these studies. Although preconception genetic carrier tests and screening have been shown to be highly accurate and efficient in determining carrier status (Bach 2001; CDC 2004; Peters 2012; Weatherall 1997), the effectiveness of such interventions is to enable reproductive choice for carrier couples, which may, as a consequence, lead to reduced morbidity and mortality of the diseases. Therefore, reproductive outcomes are essential to addressing this question. Adequately-powered RCTs assessing reproductive outcomes (number of affected children born with genetic conditions) and reproductive decision outcomes on future conception (termination, *in vitro* fertilisation, use of donor gametes, adoption, or refraining from having children) are ideal to better inform recommendations for clinical practice. Any self-reported secondary outcome measures need to use validated instruments. These trials will require longer durations of follow-up than previous studies, starting from pre-pregnancy and lasting into the post-natal period.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alhamdan 2007	Participants: couples planning to marry and applying for marriage licence Intervention: premarital screening programme for sickle cell and beta-thalassemia Comparator: none Outcome: number confirmed sickle cell and beta thalassemia carriers, decision for marriage Design: observational, cross-sectional study Excluded due to non-RCT design
Archibald 2017	Participants: woman prior to pregnancy or early in pregnancy (recommended ≤ 12 weeks gestation) Intervention: simultaneous genetic carrier testing for CF, FXS and SMA Comparator: none

Study	Reason for exclusion
	Outcome: number of carriers for CF, FXS and SMA Design: observational, cross-sectional Excluded due to non-RCT study design
Bekker 1993	Participants: adults 18 - 45 years Intervention: genetic carrier testing for cystic fibrosis Comparator: none Outcome: anxiety Design: observational, before and after intervention study Excluded due to non-RCT study design
Castellani 2011	Participants: infertile couples undergoing cystic fibrosis screening as part of assisted reproduction process Intervention: genetic counselling via computer program Comparator: standard care genetic counselling session Outcome: knowledge Design: RCT Excluded because intervention was method of delivering genetic counselling and not preconception genetic carrier testing or screening compared to standard care
Cheuvront 1998	Participants: relatives of people with CF Intervention: home-based pretest education from pamphlet with genetic test Comparator: clinic based pretest education via genetic counselling with genetic test Outcome: anxiety, knowledge, satisfaction, reproductive intent Design: RCT Excluded because intervention was method of delivering genetic counselling and not preconception genetic carrier testing or screening compared to standard care
Childs 1976	Participants: carriers of Tay-Sachs disease identified prospectively or retrospectively during population screening Intervention: genetic carrier population screening Comparator: none Outcomes: knowledge, attitudes, anxiety, concerns, satisfaction Design: observational, cross-sectional Excluded due to non-RCT study design
Clayton 1996	Participants: non-pregnant adults visiting clinical and non-clinical sites Intervention: genetic carrier testing for CF Comparator: none

Study	Reason for exclusion
	Outcome: attitudes, beliefs Design: observational, before and after intervention design Excluded due to non-RCT study design
Fan 2018	Participants: adults > 18 years old with no known carriers status Intervention: educational online module for carrier screening for Tay Sach disease Comparator: in person genetic counselling Outcome: post-interventional genetics knowledge, perception of genetic risk score and anxiety score Design: RCT Excluded due intervention is not preconception genetic carrier testing or screening and participants are not known carrier status
Fisher 1981	Participants: adults carriers of beta-thalassaemia 18 - 65 years in a HMO Intervention: genetic counselling through video Comparator: conventional counselling by a trained physician Outcome: knowledge, sexual activity, mood change, behaviour, anxiety Design: RCT Excluded because the intervention is not preconception genetic carrier testing or screening
Hegwer 2006	Participants: adults of Ashkenazi Jewish background in prenatal and preconception settings Intervention: genetic carrier screening and education programme for Tay-Sachs disease Comparator: none Outcome: knowledge, concern, attitudes, perceptions of genetic risk Design: observational, before and after intervention Excluded due to non-RCT study design
Henneman 2001	Participants: adults aged 20 - 35 years invited through Municipal Health Service or General Practitioner Intervention: genetic carrier screening for cystic fibrosis Comparator: none Outcome: knowledge, attitudes, understanding, satisfaction, psychological well-being, uptake, worry, reproductive intentions, sharing of information Design: observational, before and after intervention Excluded due to non-RCT study design
Honnor 2000	Participants: adults 18 - 50 years in a primary care setting Intervention: genetic carrier testing and counselling for cystic fibrosis Comparator: none

Study	Reason for exclusion
	Outcome: anxiety, knowledge Design: observational, before and after intervention Excluded due to non-RCT study design
Moudi 2016	Participants: couples went for pre-marital counselling center Intervention: motivational interviewing before carrier screening for thalassaemia Comparator: usual care Outcome: screening rate Design: RCT Excluded due intervention is not preconception genetic carrier testing or screening and partcipants are not known carrier status
Payne 1997	Participants: adults 16 - 45 years in a primary care practice in South Wales Intervention: genetic carrier testing for CF Comparator: none Outcome: knowledge, anxiety Design: observational, before and after intervention Excluded due to non-RCT study design
Punj 2018	Participants: women planning a pregnancy Intervention: genome sequencing of the expanded genetic screening program Comparator: screening for CF Outcome: number of variants reported Design: RCT Excluded due intervention is not preconception genetic carrier testing or screening and participants are not known carrier status
Quigley 2018	Participants: parents of children who were identified as increased risk of CF following newborn screening programme Intervention: information pack on CF Comparator: no information pack on CF Outcome: knowledge and stress score Design: RCT Excluded due intervention is not preconception genetic carrier testing or screening
Rémus 2020	Participants: parents of children who were identified SCD carrier following newborn screening programme Intervention: methods for invitation to come for screening: letter and a follow-up phone call; letter and 3 follow-up text messages within 5 days.

Study	Reason for exclusion
	Comparator: invitation by letter only Outcome: screening rate Design: RCT Excluded due intervention is not preconception genetic carrier testing or screening
Sallevalt 2021	Participants: consanguineous couples Intervention: exome sequencing of preconception carrier testing Comparator: none Outcome: variants from exome-sequencing and preconception carrier testing gene panel analysis Design: cross-sectional study Excluded due to non-RCT study design and intervention is not preconception genetic carrier testing or screening
Tambor 1994	Participants: adults 18 - 44 years in a HMO Intervention: invitation offering CF carrier screening and information giving either by personal education on-site or by mailed brochure Comparator: none Outcome: attitudes, tolerance, utilization Design: observational, before and after intervention Excluded due to non-RCT study design
Temme 2015	Participants: parents of infants with positive newborn screening results for CF and one identified *CFTR* mutation Intervention: genetic counselling plus a 4-minute video on CF Comparator: genetic counselling only Outcome: knowledge: understanding of carrier status, autosomal recessive inheritance, the newborn screening process, and symptoms of CF Design: RCT Excluded due to intervention being the method of delivering genetic counselling and education and not preconception genetic carrier testing or screening
Watson 1991	Participants: adults 16 - 44 years from primary care practices and family planning clinics Intervention: genetic carrier testing for CF Comparator: none Outcome: anxiety, response to positive results, knowledge, reproductive intentions, behaviour Design: observational, before and after intervention Excluded due to non-RCT study design
Wilkie 2013	Participants: adults 18 - 35 years with sickle cell disease or sickle cell trait from clinics and community settings

Study	Reason for exclusion
	Intervention: web-based multimedia educational intervention Comparator: usual care information e-book Outcome: knowledge, reproductive intent and behaviour Design: RCT Excluded because the intervention was the delivery of education and not preconception genetic carrier testing or screening

CF: cystic fibrosis
FXS: fragile X syndrome
SCD: sickle cell disease
HMO: health maintenance organisation
RCT: randomised controlled trial
SMZ: spinal muscular atrophy

APPENDICES

Appendix 1. Glossary

Term	Explanation
Antenatal	A period during pregnancy and before birth of the child.
Ancestry	A person's ethnic origin or descent.
Atelectasis	A collapsed portion of the lung which does not contain air. This can be caused by excessive accumulations of mucous secretions, inhaled foreign bodies or bronchial cancers.
Autosomal recessive genetic disorders	A genetic trait or disorder which appears only when an individual inherits a pair of chromosomes, each containing the gene for the trait. One chromosome of the pair comes from the father and the other from the mother. Autosomal recessive disorders can occur only if both parents are carriers of the trait.
Bronchiectasis	Persistent and progressive dilation of bronchi (branches from the trachea which lead to the lungs) often as a consequence of inflammatory disease (lung infections).
Carrier (in genetics)	An individual who possesses one copy of a mutated allele that causes disease only when two copies are present (an autosomal recessive genetic disorders). A carrier is not affected by the disease, but two carriers can produce a child with the disease.
Chronic vaso-occlusion	Blockage of arteries marked by long duration, by frequent recurrence over a long time, and often by slowly progressing deterioration; having a slow progressive course of indefinite duration.
Cystic fibrosis transmembrane conductance regulator (CFTR)	A protein, involved in the movement of salt across cell membranes, which is lacking or does not function normally in people with cystic fibrosis.
Diabetes mellitus	A pancreatic disorder that causes abnormal insulin production. This affects the body's ability to utilise sugar and other food substances and is usually treated by diet modification (restricted sugar intake) and use of insulin.

(Continued)

DNA (Deoxyribonucleic acid)	The chemical coding for a gene. DNA determines the 'genetic message' within each cell, organ, and organism.
Electrophoresis	A method of separating particles relative to a fluid under the influence of a spatially uniform electric field.
Ethnicity	Common characteristics of people of a distinct national, racial or cultural group.
Gangliosides	A group of glysolipid cells that are found in the brain.
Gene	The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein.
Globin chains	Blood proteins found in red blood cells that are combined to make haemoglobin. They are α or β globin chains.
Haemoglobin A	Normal adult haemoglobin.
Haemoglobin F	A kind of haemoglobin usually present during fetal (intrauterine) life, which has a different chemical structure from normal adult haemoglobin. After birth, the fetal haemoglobin in the red blood cells is gradually replaced by the adult type of haemoglobin, this process is usually complete during the first six months of life.
Haemolysis	Breaking of the red cell membrane causing release of haemoglobin.
Haemolytic anaemia	A condition where there are fewer red blood cells than average circulating in the blood stream due to breaking of the red cell membrane causing release of haemoglobin.
Hexosaminidase A isozyme	A protein found in the nerve cells of the brain which does not function normally in people with Tay-Sachs disease.
High performance liquid chromatography (HPLC)	A method that is used to separate a mixture of compounds to identify and quantify the individual components of the mixture.
Hypothyroidism	Results from a deficiency of thyroid hormone, and is characterized by a decrease in basal metabolic rate and by tiredness, lethargy and sensitivity to cold.
In vitro fertilization	A technique by which eggs are collected from a woman and fertilised with a man's sperm outside the body. Usually one or two resulting embryos are then transferred to the womb. If one or more of them implants successfully in the womb it results in a pregnancy.
In vivo	Inside the living body.
Mutation	A change or alteration of the DNA sequence within a gene.
Nasal epithelium	The tissue that covers and lines the surface of the nose.
Obstructive azoospermia	A condition where there is no measurable sperm detected in the semen due to ejaculatory dysfunction or ductal blockage. This condition can occur in people with cystic fibrosis.
Pancreatic exocrine insufficiency	A condition characterized by deficiency of the pancreatic enzymes, resulting in the inability to digest food properly, or maldigestion.
Salt-loss syndromes	A condition found in people with cystic fibrosis where there is loss of salt resulting in depletion of salt in the body.

(Continued)

Septicaemia	A condition characterized by the widespread destruction of tissues due to absorption of disease containing bacteria or their toxins from the bloodstream.

For further statistical terms, please refer to the The Cochrane Collaboration Glossary (http://cochrane.org/glossary).

For technical or clinical terms, please refer to The Human Genetics Commission Glossary (http://webarchive.nationalarchives.gov.uk/20100419143351/hgc.gov.uk/client/content.asp?contentid=729).

Appendix 2. Search strategies

Database or resource	Date searched	Search strategy
Ovid MEDLINE(R) Daily Update Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)	1970 to 25 June 2021	1. exp Thalassemia/ 2. thalass?emia.ti,ab,ot,hw. 3. ((erythroblastic or erythro-blastic or hypochromic or cooley$ or mediterranean) adj2 an?emia$).ti,ab,ot,hw. 4. (h?emoglobin adj2 disease$).ti,ab,ot,hw. 5. exp Hemoglobinopathies/ 6. hereditary persistence of f?etal h?emoglobin.ti,ab,ot,hw. 7. (h?emoglobin adj2 (H or F or D or E) adj2 disease$).ti,ab,ot,hw. 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 9. exp Anemia, Sickle Cell/ 10. Sickle Cell Disease.ti,ab,ot,hw. 11. (sickle cell adj2 (an?emia$ or disease$ or disorder$)).ti,ab,ot,hw. 12. (h?emoglobin adj2 (S or C or SC)).ti,ab,ot,hw. 13. ((drepanocytosis or drepanocytic) adj2 an?emia).ti,ab,ot,hw. 14. 9 or 10 or 11 or 12 or 13 15. Cystic Fibrosis/ 16. cystic fibrosis.ti,ab,ot,hw. 17. CF.ti,ab. 18. mucoviscidosis.ti,ab,ot,hw. 19. (fibrocystic adj3 disease$).ti,ab,ot,hw. 20. (pancreas$ adj2 (fibrosis or cystic disease$)).ti,ab,ot,hw. 21. 15 or 16 or 17 or 18 or 19 or 20 22. Tay-Sachs Disease/ 23. Tay Sachs.ti,ab,ot,hw. 24. ((familial or infantile) adj2 amaurotic idiocy).ti,ab,ot,hw.

(Continued)

25. TSD.ti,ab.

26. (GM2 adj2 gangliosidosis).ti,ab,ot,hw.

27. 22 or 23 or 24 or 25 or 26

28. Heterozygote/

29. trait$.ti,ab,ot,hw.

30. carrier$.ti,ab,ot,hw.

31. 28 or 29 or 30

32. 8 or 14 or 21 or 27 or 31

33. (Preconcept$ or Pre-concept$ or Prepregnan$ or Pre-pregnan$).ti,ab,ot,hw.

34. Maternal Health Services/

35. ((pregnan$ or conception or family) adj3 plan$).ti,ab,ot,hw.

36. (Pre-marital or Premarital or Pre-marriage or Premarriage).ti,ab,ot,hw.

37. ((Preconcept$ or Pre-concept$ or Prepregnan$ or Pre-pregnan$) adj2 (care or counsel$ or advice$ or advise or inform$)).ti,ab,ot,hw.

38. ((Pre-marital or Premarital or Pre-marriage or Premarriage) adj2 (care or counsel$ or advice$ or advise or inform$)).ti,ab,ot,hw.

39. 33 or 34 or 35 or 36 or 37 or 38

40. (carrier$ adj3 (screen$ or test$ or counsel$ or assess$ or detect$ or diagnos$ or inform$ or analys$)).ti,ab,ot,hw.

41. (genetic$ adj3 (screen$ or test$ or counsel$ or assess$ or detect$ or diagnos$ or inform$ or analys$)).ti,ab,ot,hw.

42. (heterozygot$ adj3 (screen$ or test$ or counsel$ or assess$ or detect$ or diagnos$ or inform$ or analys$)).ti,ab,ot,hw.

43. Genetic Services/

44. family history.ti,ab,ot,hw.

45. 40 or 41 or 42 or 43 or 44

46. (h?emoglobin adj2 electrophoresis).ti,ab,ot,hw.

47. Cystic Fibrosis Transmembrane Conductance Regulator/ or sweat test.ti,ab,ot,hw.

48. ((CFTR gene mutation$ or CFTR mutation$ or Hexoaminidase-A or Hexoaminidase A or HEX-A or H?emoglobin F or H?emoglobin A2 or H?emoglobin S) adj3 (test$ or analys$ or screen$ or profil$)).ti,ab,ot,hw.

49. 46 or 47 or 48

50. 32 or 45 or 49

51. 39 and 50

52. exp animals/ not humans.sh.

53. 51 not 52

(Continued)

		54. limit 53 to yr="1970-Current"
PsycINFO	1970 to 25 June 2021	1. thalassemia.ti,ab,ot,hw. 2. thalassaemia.ti,ab,ot,hw. 3. ((erythroblastic or erythro-blastic or hypochromic or cooley* or mediterranean) adj2 anaemia*).ti,ab,ot,hw. 4. ((erythroblastic or erythro-blastic or hypochromic or cooley* or mediterranean) adj2 anemia*).ti,ab,ot,hw. 5. ((haemoglobin or hemoglobin) adj2 disease*).ti,ab,ot,hw. 6. ((haemoglobin or hemoglobin) adj2 (H or F or D or E) adj2 disease*).ti,ab,ot,hw. 7. 1 or 2 or 3 or 4 or 5 or 6 8. Sickle Cell Disease/ 9. (sickle cell adj2 (anaemia* or disease* or disorder*)).ti,ab,ot,hw. 10. ((haemoglobin or hemoglobin) adj2 (S or C or SC)).ti,ab,ot,hw. 11. 8 or 9 or 10 12. Cystic Fibrosis/ 13. cystic fibrosis.ti,ab,ot,hw. 14. CF.ti,ab. 15. mucoviscidosis.ti,ab,ot,hw. 16. (fibrocystic adj3 disease*).ti,ab,ot,hw. 17. 12 or 13 or 14 or 15 or 16 18. Tay Sachs Disease/ 19. Tay Sachs.ti,ab,ot,hw. 20. ((familial or infantile) adj2 amaurotic idiocy).ti,ab,ot,hw. 21. TSD.ti,ab. 22. (GM2 adj2 gangliosidosis).ti,ab,ot,hw. 23. 18 or 19 or 20 or 21 or 22 24. heterozygote.ti,ab,ot,hw. 25. trait*.ti,ab,ot,hw. 26. carrier*.ti,ab,ot,hw. 27. 24 or 25 or 26 28. 7 or 11 or 17 or 23 or 27 29. (Preconcept* or Pre-concept* or Prepregnan* or Pre-pregnan*).ti,ab,ot,hw. 30. (Pre-marital or Premarital or Pre-marriage or Premarriage).ti,ab,ot,hw. 31. maternal health service*.ti,ab,ot,hw.

(Continued)

		32. maternal care.ti,ab,ot,hw. 33. ((pregnan* or conception or family) adj3 plan*).ti,ab,ot,hw. 34. ((Preconcept* or Pre-concept* or Prepregnan* or Pre-pregnan*) adj2 (care or counsel* or advice* or advise or inform*)).ti,ab,ot,hw. 35. ((Pre-marital or Premarital or Pre-marriage or Premarriage) adj2 (care or counsel* or advice* or advise or inform*)).ti,ab,ot,hw. 36. 29 or 30 or 31 or 32 or 33 or 34 or 35 37. (genetic* adj3 (screen* or test* or counsel* or assess* or detect* or diagnos* or inform* or analys*)).ti,ab,ot,hw. 38. (carrier* adj3 (screen* or test* or counsel* or assess* or detect* or diagnos* or analys*)).ti,ab,ot,hw. 39. (heterozygot* adj3 (screen* or test* or counsel* or assess* or detect* or diagnos* or analys*)).ti,ab,ot,hw. 40. genetic service*.ti,ab,ot,hw. 41. family history.ti,ab,ot,hw. 42. 37 or 38 or 39 or 40 or 41 43. ((haemoglobin or hemoglobin) adj2 electrophoresis).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] 44. Cystic Fibrosis Transmembrane Conductance Regulator/ or sweat test.mp. 45. 43 or 44 46. 28 or 42 or 45 47. 36 and 46 48. exp Animals/ 49. human.mp. 50. 48 and 49 51. 48 not 50 52. 47 not 51 53. limit 52 to yr="1970-Current"
Embase	1974 to 25 June 2021	1. exp thalassemia/cn, di, ep, et, pc [Congenital Disorder, Diagnosis, Epidemiology, Etiology, Prevention] 2. exp delta thalassemia/ or exp beta thalassemia/ or exp thalassemia major/ or exp alpha thalassemia/ or exp thalassemia intermedia/ or exp sickle cell beta thalassemia/ or exp thalassemia minor/ 3. thalass?emia.ti,ab,ot,hw. 4. ((erythroblastic or erythro-blastic or hypochromic) adj2 an?mia $).ti,ab,ot,hw. 5. (h?emoglobin adj2 disease$).ti,ab,ot,hw.

(Continued)

6. hemoglobinopathy/cn, di, ep, et, pc [Congenital Disorder, Diagnosis, Epidemiology, Etiology, Prevention]

7. hereditary persistence of f?etal h?emoglobin.ti,ab,ot.

8. (h?emoglobin adj2 (h or d or e) adj2 disease$).ti,ab,ot,hw.

9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10. exp sickle cell anemia/cn, di, ep, et, pc [Congenital Disorder, Diagnosis, Epidemiology, Etiology, Prevention]

11. sickle cell disease.ti,ab,ot,hw.

12. (h?emoglobin adj2 (s or c)).ti,ab,ot,hw.

13. 10 or 11 or 12

14. exp cystic fibrosis/cn, di, ep, et, pc [Congenital Disorder, Diagnosis, Epidemiology, Etiology, Prevention]

15. cystic fibrosis.ti,ab,ot,hw.

16. CF.ti,ab.

17. 14 or 15 or 16

18. exp Tay Sachs disease/cn, di, ep, et, pc [Congenital Disorder, Diagnosis, Epidemiology, Etiology, Prevention]

19. Tay Sachs.ti,ab,ot,hw.

20. ((familial or infantile) adj2 amaurotic idiocy).ti,ab,ot,hw.

21. TSD.ti,ab.

22. 18 or 19 or 20 or 21

23. exp heterozygote/ or exp heterozygote detection/

24. trait$.ti,ab,ot,hw.

25. carrier$.ti,ab,ot,hw.

26. 23 or 24 or 25

27. 9 or 13 or 17 or 22 or 26

28. (Preconcept$ or Pre-concept$ or Prepregnan$ or Pre-pregnan$).ti,ab,ot,hw.

29. (Pre-marital or Premarital or Pre-marriage or Premarriage).ti,ab,ot,hw.

30. ((pregnan$ or conception or family) adj3 plan$).ti,ab,ot,hw.

31. ((Preconcept$ or Pre-concept$ or Prepregnan$ or Pre-pregnan$) adj2 (care or counsel$ or advice$ or advise or inform$)).ti,ab,ot,hw.

32. ((Pre-marital or Premarital or Pre-marriage or Premarriage) adj2 (care or counsel$ or advice$ or advise or inform$)).ti,ab,ot,hw.

33. 28 or 29 or 30 or 31 or 32

34. (carrier$ adj3 (screen$ or test$ or counsel$ or assess$ or detect$ or diagnos$ or inform$ or analys$)).ti,ab,ot,hw.

(Continued)

		35. (genetic$ adj3 (screen$ or test$ or counsel$ or assess$ or detect$ or diagnos$ or inform$ or analys$)).ti,ab,ot,hw. 36. (heterozygot$ adj3 (screen$ or test$ or counsel$ or assess$ or detect$ or diagnos$ or inform$ or analys$)).ti,ab,ot,hw. 37. Genetic Service$.ti,ab,ot,hw. 38. family history.ti,ab. 39. 34 or 35 or 36 or 37 or 38 40. (h?emoglobin adj2 electrophoresis).ti,ab,ot,hw. 41. Cystic Fibrosis Transmembrane Conductance Regulator.ti,ab,ot,hw. 42. sweat test.ti,ab. 43. ((CFTR gene mutation$ or CFTR mutation$ or Hexoaminidase-A or Hexoaminidase A or HEX-A or H?emoglobin F or H?emoglobin A2 or H?emoglobin S) adj3 (test$ or analys$ or screen$ or profil$)).ti,ab,ot,hw. 44. 40 or 41 or 42 or 43 45. 27 or 39 or 44 46. 33 and 45 47. animal/ 48. human/ 49. 47 and 48 50. 47 not 49 51. 46 not 50 52. limit 51 to yr="1970-Current"
CINAHL	1970 to 25 June 2021	SI. (MH "Thalassemia") OR (MH "beta-Thalassemia") OR (MH "alpha-Thalassemia") OR (MH "delta-Thalassemia") S2. (MH "Hemoglobinopathies") S3. (MM "Anemia, Hypochromic") S4. (MH "Anemia, Sickle Cell") OR (MH "Sickle Cell Trait") S5. (MH "Cystic Fibrosis") OR "mucoviscidosis" S6. (MH "Tay-Sachs Disease") S7. (MH "Prepregnancy Care") S8. (MH "Genetic Screening") S9. (MH "Family Assessment") OR (MH "Family History") S10. "hemoglobin electrophoresis" S11. "cystic fibrosis transmembrane conductance regulator" S12. "sweat test" S13. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S8 OR S9 OR S10 OR S11 OR S12

(Continued)

		S14. S7 AND S13 S15. Limiters - Published Date from: 19700101-current
National Institutes of Health database (clinicaltrials.gov/)	2005 to 25 June 2021	preconception OR prepregnancy OR premarital
Clinical Trials Search Portal of the World Health Organization (apps.who.int/trialsearch/)	2004 to 25 June 2021	preconcep* OR prepregnan* OR premarital
Current Controlled Trials in the metaRegister of controlled clinical trials (www.controlled-trials.com/)	2004 to 25 June 2021	"preconception OR prepregnancy OR premarital"

WHAT'S NEW

Date	Event	Description
16 August 2021	New search has been performed	A search of the Group's Trials Registers identified seven new references potentially eligible for inclusion in the review; three of these were additional references to an already excluded study (Wilkie 2013) and the remaining four were not even suitable to be listed as excluded studies and were immediately discarded. Additional planned searches of databases and key journals identified nine new references potentially eligible for inclusion in the review. One of these was the full paper to a study previously listed as ongoing, but which has now been excluded (Punj 2018). All of the remaining eight references to six studies were excluded as they did not meet the review's eligibility criteria (Archibald 2017; Fan 2018; Moudi 2016; Quigley 2018; Rémus 2020; Sallevalt 2021). We have added plans for generating a summary of findings table for each comparison, which we may be able to present in future updates of the review, to the Methods section in line with current Cochrane guidance. We have added a third primary outcome to assess the number of women or couples who make an informed choice measured by tools such as the Multidimensional Measure of Informed Choice (MMIC).
16 August 2021	New citation required but conclusions have not changed	No new data have been added to the review. However, we have added suggestion for future searches in our conclusions. A new author, Professor Lidewij Henneman, has joined the team; Professor Jos Kleijnen and Dr Stephen Weng have left the review team.

HISTORY

Protocol first published: Issue 12, 2013
Review first published: Issue 8, 2015

Date	Event	Description
25 January 2018	New citation required but conclusions have not changed	No new data have been added to the review so our conclusions remain the same.
25 January 2018	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Review Group's trials registers identified two references to a single trial which has been excluded (Temme 2015). A search from MEDLINE identified one reference which was potentially eligible for inclusion in the review and has been listed as ongoing until completed (Kauffman 2017a).

CONTRIBUTIONS OF AUTHORS

Writing the protocol: all authors
Developing the search strategy: NH, NQ, JK and other (not review authors)
Searching for trials: NH, LH and NQ
Selection of trials: NH, LH, NQ, and other (not review authors)
Data entry: NH
Analysis: NH, LH and NQ
Interpret analysis: all authors
Draft final review: all authors
Update the review: NH, LH and NQ

DECLARATIONS OF INTEREST

Dr Norita Hussein has no known interest to declare.

Dr Nadeem Qureshi is an investigator on a UK National Institute of Health research project evaluating preconception screening in primary care and plan to pursue further research in this area. Dr Qureshi is also collaborating on a project to evaluate the evidence base relevant to NICE guidelines behind primary care. In February 2019, he received an honorarium and travel expenses for a lecture from Amgen Inc.

Professor Hennemann declares she has worked on several pilot studies for carrier screening, which are not eligible for inclusion in the review. She received a research grant from the Netherlands Organisation for Health Research and Development (ZonMw) to study: "Preconception carrier screening in the Netherlands: Advantages and consequences, societal support and ethical framework". She is an unpaid member of the Dutch Working Group for Preconception Carrier Screening and a member of the Advisory Board for the Association of Clinical Genetics Netherlands (VKGN). She is affiliated to the University Hospital Amsterdam UMC that offers expanded carrier in a non-commercial setting.

Dr Joe Kai was an investigator on the UK National Institute of Health research project evaluating preconception screening in primary care up to December 2019, but currently has no known interest to declare.

SOURCES OF SUPPORT

Internal sources

- University of Nottingham, UK

  The university provided computer and internet access.

External sources

- National Institute for Health Research, UK

  This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Handsearching of key journals was originally specified from 1984 to date in the protocol. In the review, handsearching was conducted from 1998 to date for the *European Journal of Human Genetics* and *Genetics in Medicine* and from 2010 to date for the *Journal of Community Genetics.* This change was made because these were the earliest dates that the online tables of contents were accessible for these key journals.

We have added plans for summary of findings tables to the Methods.

We have added a third primary outcome to assess the number of women or couples who make an informed choice measured by tools such as the Multidimensional Measure of Informed Choice (MMIC).

INDEX TERMS

Medical Subject Headings (MeSH)

Anemia, Sickle Cell [*genetics]; Cystic Fibrosis [*genetics]; *Genetic Carrier Screening; *Preconception Care; Risk Assessment; Tay-Sachs Disease [*genetics]; Thalassemia [*genetics]

MeSH check words

Female; Humans