A systematic review of psycho-social interventions for individuals with a BRCA1/2 pathogenic variant

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Abstract
Women with a pathogenic variant in BRCA1/2 genes have up to an 87% lifetime risk of breast cancer and up to a 68% lifetime risk for ovarian cancer. Common risk-reducing measures include prophylactic surgeries or pharmacological approaches, such as chemoprevention. Psycho-social issues can arise due to this increased risk, often resulting in heightened distress or anxiety. This review examines the efficacy of interventions aimed at improving psychological adjustment in individuals with a pathogenic variant in BRCA1/2. A Public and Patient Involvement (PPI) Panel of six individuals with a BRCA1/2 pathogenic variant provided input on the terminology used and dissemination of the review. Interventions assessing psychological measures in BRCA1/2 pathogenic variant carriers, published in English, were considered eligible for inclusion. A systematic search strategy was carried out on OVID, EBSCO, Cochrane Library, PubMed, Web of Science Core Collections, and Scopus. Two independent reviewers conducted screening, data extraction, risk of bias assessments, and theory coding. Findings were reported through narrative synthesis. Of the 1,024 results from searches, fifteen interventions were eligible. Nine of these were randomized controlled trials, six were quasi-experimental. There was heterogeneity in intervention design, with limited evidence of improvement upon psychological outcome measures. No study was rated as being low risk for bias. Five studies obtained the highest level of risk for bias, the majority of issues arising from problematic outcome measurement. No single study met all criteria on the Theory Coding Scheme, with five studies mentioning a theoretical aspect to intervention design, of which three employed a middle-range theory only. Some studies demonstrated a longitudinal impact on outcomes, however, there is insufficient evidence to draw broad conclusions from this. Further research is needed to better develop interventions to support those with a pathogenic variant in BRCA1/2 throughout their coping experience.

Keywords
anxiety, BRCA1/2, distress, intervention, stress, systematic review
1 | INTRODUCTION

Women that carry a *BRCA1/2* pathogenic variant are at a significantly increased risk of developing certain cancers in their lifetime. The cumulative lifetime risk of breast cancer ranges between 40% – 87% for women with a *BRCA1* pathogenic variant, and an ovarian cancer risk of 16% – 68% (Kuchenbaecker et al., 2017). There is similar risk for women with a *BRCA2* pathogenic variant, with a 27% – 84% lifetime breast cancer risk, and 11% – 30% ovarian cancer risk (Kuchenbaecker et al., 2017). To reduce these cancer risks, it is advised that women undergo risk-reducing measures, of which the most common are surgical, namely prophylactic double mastectomies, and prophylactic salpingo-oophorectomies, usuallycommencing between the ages of 30 – 40. Pharmacological methods are also available, specifically chemoprevention for breast cancer risk reduction, and the oral contraceptive pills for reducing ovarian cancer risk (Bermejo-Pérez et al., 2007; Friefel et al., 2014).

At present, there is contradictory literature detailing the psychological coping trajectory experienced by *BRCA1/2* pathogenic variant carriers. Past meta-analytic research noted that the distress experienced by this population did not reduce exponentially, and rather there was a limited natural decrease in levels of distress over time (Meiser & Halliday, 2002). A more recent meta-analysis (Hamilton et al., 2009) concluded that while rates of distress and anxiety did increase in the timeframe immediately post-test results (0–4 weeks), these returned to baseline levels after a moderate (5–24 weeks) or long (25–52 weeks) period. Hamilton et al., (2009) further discuss that while levels did return to baseline after some time, baseline levels of cancer-specific distress were higher than that of the general population. This was not the case for anxiety, with levels being similar to general population rates.

Furthermore, little research has been conducted on the differing intervention methods that target psycho-social well-being in this population. A recent Cochrane systematic review did assess this, however, it focused only on the time frame following prophylactic salpingo-oophorectomy (Jeffers et al., 2017). The current systematic review is the first to assess interventions that emphasize psychological, behavioral, or social factors rather than physiological factors in a *BRCA1/2* pathogenic variant population, that aim to promote adjustment and improve psychological outcomes. Adjustment is defined in terms of alleviating stress, anxiety, depression and distress, and enhancing coping and knowledge of risk perceptions in those with a known *BRCA1/2* pathogenic variant. This review assessed these, with input from the target population, and further evaluation of theory use, detailed below.

1.1 | Patient and public involvement

It is broadly agreed upon that addition of Patient and Public Involvement (PPI) can help improve the impact and relevance of studies in fields such as health research (Pollock et al., 2018). The inclusion of stakeholders of the target population under study can assist in bridging the research-implementation gap through the co-creation of knowledge between the researcher and those being researched (Heaton et al., 2015; Pollock et al., 2018). Given the frequency with which systematic reviews are utilized to inform both research plans and policy change, it is paramount that the views of the population at hand are at the forefront of research design. This review incorporated the involvement of a PPI panel who provided input on the communication and dissemination of review findings.

What is known about this topic
Pathogenic variants in *BRCA1* and *BRCA2* result in heightened lifetime risk of cancers, primarily in breast and ovarian cancer in females. This increased risk can contribute toward psychological distress of the individual carrying such a variant.

What this paper adds to this topic
This systematic review is the first to synthesize interventions which aimed to address psychological adjustment, measured as outcomes of distress, anxiety, stress, and coping. It demonstrates that there are currently limited high-quality interventions, designed with attention to relevant theories in this area - signifying the need for further research.

1.2 | Theory use

In prior psycho-oncology research, the use of theory in interventions has been associated with improved intervention effectiveness (Bluethmann et al., 2017). There has been no investigation into the use of theory in intervention development and design in this field as of yet. Therefore, the current review, through use of a behavioral science tool — The Theory Coding Scheme (TCS; Michie & Prestwich, 2010), assesses whether there were any theoretical underpinnings in the included studies. The TCS is a mechanism providing a means through which the theoretical structure of interventions can be assessed, and has been previously highlighted as a tool which can be employed in an evidence synthesis methodology (Michie & Prestwich, 2010).

This review will aim to explore the current available evidence to synthesize the various interventions aimed at improving psychological adjustment in individuals with a *BRCA1* or *BRCA2* pathogenic genetic variant, with a secondary aim of summarizing the theories utilized in intervention design.

2 | METHODS

A protocol for the systematic review was registered on PROSPERO (see: https://www.crd.york.ac.uk/PROSPERO/display_record.php?)
RecordID=139546). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher et al., 2009) were used to inform the review procedure and reporting (see Appendix SA).

2.1 | Eligibility criteria

Studies were included if they were psychological or psycho-social interventions aimed at improving psychological adjustment in individuals with a pathogenic variant in BRCA1/2. Studies were required to include adult participants (>18 years) post-genetic testing — participants must have been aware of their BRCA1/2 pathogenic variant carrier status prior to intervention commencement. A restriction of papers published in English after 1990 (when the BRCA1/2 gene was discovered to be relevant in hereditary cancers) was applied. Studies that sampled individuals prior to their pathogenic variant result were excluded. Only experimental studies (randomized controlled trials) and quasi-experimental studies were included in this review. Papers were included that assessed one or more psychological or psycho-social variable (e.g., distress, quality of life, and anxiety) as an outcome.

2.2 | Search Strategy

An OVID Medline search strategy (see Appendix SB) was compiled by NW, and was checked and revised by an expert research support librarian before translating into specific search strategies for each database. The search strategy was based on two main concepts: hereditary breast and ovarian cancer terms related to BRCA1/2, and terms related to psychological adjustment, distress, and quality of life. The following electronic databases were searched OVID (MEDLINE(R), PsycINFO, PsycExtra, Access PsycARTICLES, Journals @ Ovid Full Text, Your Journals @ Ovid), EBSCO (CINAHL, Psychology and Behavioral Science Collection), Cochrane Library, PubMed, Web of Science Core Collections, and Scopus. Forward citation searches (screening articles that have cited any of the included articles) and backward citation searches (screening the reference list of included papers) were conducted on all articles that were included after full-text screening. Conference abstracts for the following sources from 1990 onward were also searched: Irish Society of Human Genetics and European Society of Human Genetics.

2.3 | Assessment of study eligibility

Duplicates were removed using EndNote X8. Searches were then uploaded to Rayyan QCRI (Ouzzani et al., 2016), an open-source website designed for screening papers for systematic reviews, wherein a second screening for duplicates was conducted. All further screening was then conducted utilizing the Rayyan QCRI software to allow for independent screening of papers.

A single reviewer (NW) initially screened titles to remove papers that were deemed irrelevant (e.g., those with a complete medical/pharmaceutical focus). Abstract screening followed, whereby two reviewers (NW and SM) worked independently on screening all remaining abstracts, categorizing them as ‘include’, ‘exclude’, or ‘unsure’. Full texts of those classified as ‘include’ and ‘unsure’ were then screened and assessed for eligibility in duplicate (NW and SM). Disagreements were resolved through discussion between the two reviewers, and a third reviewer (AMG) resolved any differences.

2.4 | Data extraction

The following data were extracted for each paper by two reviewers (NW and SM) using a standardized data extraction form on Microsoft Excel: author/year published/country of publication/language, journal citation, study design/methodology/settng, study population (sample size, participant characteristics, age/gender/ethnicity/socio-economic status/education/parity, cancer diagnosis; yes or no, BRCA1 or BRCA2 pathogenic variant identified), intervention details, type of intervention, mode of delivery, who delivered, intervention duration/number of sessions, and outcomes (measures used to assess outcomes, how the outcome was defined). Disagreements between NW and SM were resolved by discussion or by getting input from a third reviewer (AMG).

2.5 | Synthesis

A meta-analysis was not deemed to be appropriate due to the small number of included studies, in which there was minimal homogeneity in design or outcome. Data are therefore presented in a narrative synthesis, following the approach proposed by Popay et al., (2006).

2.6 | Risk of bias assessment

Risk of bias was independently assessed by two reviewers (NW and SR). The included randomized controlled trials (n = 9) were assessed utilizing The Cochrane Risk of Bias Tool (Sterne et al., 2019), and the non-randomized controlled trials (n = 6) were assessed using Cochrane’s Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool (Sterne et al., 2016).

2.7 | Theory coding assessment

The use of theory in included interventions was assessed using the Theory Coding Scheme, a reliable method for assessing the extent to which behavioral interventions are theory-based (Michie & Prestwich, 2010). In line with a previous systematic review of interventions (Hennessy et al., 2019), items 11-19 of this scheme
were utilized, as these focus on the extent to which the design of an intervention was based on theory. NW and SM carried out the assessment, with input from AMG to resolve any disagreements.

2.8 | Public and patient involvement (PPI)

A PPI panel of six individuals with a BRCA1/2 pathogenic variant provided input on the dissemination of the review outside of academic journals to reach relevant patient groups. This group advised on how to disseminate the research outside of academic journals, informing on what they would find relevant and interesting from the review, and where they would go to find such information. Demographics of the panel are presented in Table S1. In addition, another group of eight women participated in a once-off consultation, hosted by the Irish Association for Cancer Research; the ‘Patient’s Voice in Cancer Research—Dragon’s Den’ event in February 2020. The participants at the Dragon’s Den event were consulted broadly on the issue around language used in reporting on the BRCA1/2 population.

3 | RESULTS

3.1 | Search results

Database searches and hand searches were completed on the 19th of September 2019. A total of 1,024 results were retrieved, 365 were duplicates, and 659 papers were screened at title and abstract stage, following which 383 papers were excluded. Finally, 176 full-text papers were screened. Thirteen papers were included and were forward and backward searched to screen for any further potentially relevant publications. Two additional papers were identified—resulting in a total of fifteen studies. All included studies were published between 2004 and 2019. Details of screening and reasons for exclusion are presented in a PRISMA flow chart (Moher et al., 2009; see Figure S1).

3.2 | Risk of bias summary

3.2.1 | Cochrane risk of bias

As shown in Figure S2, four studies (Hooker et al., 2011; Kiechle et al., 2017; Landau et al., 2015; van Roosmalen et al., 2004) were rated as being at high risk of bias, with five (van Driel et al., 2019; Graves et al., 2010; Metcalfe et al., 2017; Visser et al., 2016; White et al., 2014) being rated at moderate risk. No studies were considered to be at low risk of bias.

3.2.2 | ROBINS-I

As shown in Figure S3, four studies (Esplen et al., 2004; Landsbergen et al., 2010; Listøl et al., 2017; K. Metcalfe et al., 2007) were rated as being at moderate risk of bias, with one rated at serious risk (Bober et al., 2015). One study was considered to be at critical risk of bias (Kwiatkowski et al., 2019).

3.3 | Study design

Nine studies (60%) were randomized controlled trials, the remaining six (40%) were non-randomized studies. The included interventions were predominantly longitudinal, with only two studies utilizing a pre-post design (Landsbergen et al., 2010; Metcalfe et al., 2007). The range of follow-up times for these studies extended between immediately post-intervention (zero weeks) to 12-month post-intervention. Two studies tracked participants at just two weeks before, and two weeks after the intervention (Esplen et al., 2004; Listøl et al., 2017). One of these intervention programs lasted over one year (Esplen et al., 2004), whereas the other was a short-term study, comprised of a single group-based session (Listøl et al., 2017).

The remaining studies followed participants across a series of time points, ranging between a total of two months to 12 months. Overall, the mean follow-up time in these studies was six and a half months. Detailed information on this is displayed in Table S2, with a note of any significant changes in reported outcomes for each study time point.

3.4 | Study populations

The populations in these studies were quite homogenous. Table 1 denotes the characteristics of the population that were reported in these studies. All studies reported exclusively female participants, and none differentiated between BRCA1 or BRCA2 pathogenic variants, reporting upon it as a dichotomous (yes/no) variable, indicating whether a person did or did not harbor a pathogenic variant. Sample size in these ranged from seven to 214, with a total sample of 1,340 across all studies, with an average of 89 participants per intervention. The mean age of participants in 13 studies ranged between 26.40 and 49.63 years. One study assessed age by noting the number of people either above or below 50 (Graves et al., 2010), while another did not include information on the age of included participants (Landsbergen et al., 2010). There were limited data reporting on ethnicity/race in the studies, with only three (20%) recording such information, noting any demographic other than white, with just one specifically indicating participation of individuals from Ashkenazi Jewish heritage (7%). Most studies (60%) reported that some participants had undergone at least one preventative measure. There were reports of cancer diagnosis in the majority of studies, with 13 (87%) presenting data on breast cancer, 12 (80%) on ovarian, and five (33%) studies taking a broader approach and reporting on the presence of a diagnosis of any cancer type. No studies specifically investigated other carcinomas that are often associated with a BRCA1/2 pathogenic variant, such as colon cancer.
### 3.5 | Narrative synthesis

The included studies aimed to improve psychological functioning (e.g., anxiety and depression) through some form of intervention, although often this was not the primary objective of the study. Many provided educational content or elements of group support to their participants. Table 2 displays the components of included study characteristics.

### 3.6 | Intervention design

Many studies assessed how knowledge and decisional conflict were influenced by information provision, rather than focusing on the psychological aspects of participation in an intervention. Table 2 presents the different aspects of the included interventions, to provide a visualization of the intersection and differences between the varied approaches. There was some overlap with approach, namely that the majority, 13 (87%) studies, utilized some form of education in their method. While an effort is made to remain consistent with what corresponds to providing ‘education’, it is often unclear what researchers considered educational, and what the distinguishable foci of these were (e.g., physical health and hereditary risk). Other than educational elements, there was minimal further homogeneity within study design. Further details on study characteristics are presented in Table S3.

### 3.7 | Psychological outcomes

All studies utilized at least one measure of psychological adjustment. There was significant variation in the measures used to assess different elements of psychological adjustment, the details of these are presented in Table 3. This variation may have been a consequence of questionnaires being specifically created for the given paper, as was the case in nine (60%) of the included studies, rather than utilizing pre-validated measures.

#### 3.7.1 | Distress

Six studies utilized the Impact of Events Scale (IES) to examine distress. Of these studies, five found significant changes in IES scores, one did not (Metcalfe et al., 2007). Two studies tracked participants over 12-months (Esplen et al., 2004; Metcalfe et al., 2017) and did not find longitudinal significant results. One study trained peer-to-peer supporters to have regular contact with participants through telephone calls (White et al., 2014), and noted a significant change across time. Four interventions educated participants on BRCA1/2 pathogenic variants through different methods. One established a group therapy setting to communicate information to participants (Esplen et al., 2004), and found a significant change in distress scores, however, this was not assessed over time, as a pre-post design was utilized. Another intervention employed a shared decision-making technique (van Roosmalen et al., 2004), and reported on the IES using intrusion and avoidance subscales. While there were no significant changes in avoidant thoughts, or intrusive thoughts at three-month post-intervention, they found significant changes in intrusive thoughts at nine-month post-intervention. Two interventions utilized a decision aid (Hooker et al., 2011; Metcalfe et al., 2017). One such decision aid utilized tailored information on hereditary risk, and found a significant change in distress scores at one month, but not at six or 12-month post-intervention (Hooker et al., 2011). Similarly, the other decision aid indicated that there was a significant decrease in distress six-month post-intervention, but there were no significant changes three or 12 months after the intervention (Metcalfe et al., 2017).

#### 3.7.2 | Anxiety and depression

The Brief Symptom Inventory (BSI) was utilized in four studies. One study, which promoted the practice of relaxation training alongside mindfulness-based cognitive therapy strategies, found significant results in global severity, somatization, and anxiety two-month post-intervention, however, no changes were noted in depression (Bober et al., 2015). A study detailed above found significant changes in both anxiety and depression two-month post-intervention (Esplen et al., 2004). Two studies found no significant changes on the BSI (Hooker et al., 2011; Landau et al., 2015).

### 3.8 | Theory coding summary

The extent of theory use in the included interventions is presented in Table S4. No single study in this review met all the criteria of the...
|                                           | Bober | Driel | Esplen | Graves | Hooker | Klechle | Kwiatkowski | Landau | Landsbergen | Listøl | Metcalfe | Metcalfe | Roosmalen | Visser | White |
|------------------------------------------|-------|-------|--------|--------|--------|---------|-------------|--------|-------------|--------|----------|----------|-----------|--------|-------|
| Peer Support                             |       |       |        |        |        |         |             |        |             |        |          |          |           |        |       |
| Peer Support                             |       |       |        |        |        |         |             |        |             |        |          |          |           |        |       |
| Educational: Management Strategies       |       |       |        |        |        |         |             |        |             |        |          |          |           |        |       |
| Educational: Psychological Health        |       |       |        |        |        |         |             |        |             |        |          |          |           |        |       |
| Educational: Physical Health             |       |       |        |        |        |         |             |        |             |        |          |          |           |        |       |
| Educational: Hereditary Risk             |       |       |        |        |        |         |             |        |             |        |          |          |           |        |       |
| Educational: Other                       |       |       |        |        |        |         |             |        |             |        |          |          |           |        |       |
| Other                                    |       |       |        |        |        |         |             |        |             |        |          |          |           |        |       |
| Relaxation/Stress Reduction Training     |       |       |        |        |        |         |             |        |             |        |          |          |           |        |       |
| Exercise                                 |       |       |        |        |        |         |             |        |             |        |          |          |           |        |       |
| Group Setting                            |       |       |        |        |        |         |             |        |             |        |          |          |           |        |       |
| CBT                                      |       |       |        |        |        |         |             |        |             |        |          |          |           |        |       |
| Decision Aid                             |       |       |        |        |        |         |             |        |             |        |          |          |           |        |       |
| Telephone Counseling                     |       |       |        |        |        |         |             |        |             |        |          |          |           |        |       |
| Mindfulness                              |       |       |        |        |        |         |             |        |             |        |          |          |           |        |       |
Theory Coding Scheme, and overall scores ranged from zero to three. Three studies (20%) used the Ottawa Decision Support Framework (O’Connor et al., 1999), a middle-range theory, to design their interventions. In this instance, a middle-range theory refers to a sociological concept (Merton, 2000), indicating a theory that is utilized to guide empirical work. The Ottawa Decision Support Framework is built on empirical research, alongside theories and concepts across multiple disciplines such as social psychology, decision-making, and social support (O’Connor et al., 1999).

One study (7% of included studies) utilized the Transactional Model of Stress and Coping (Lazarus & Folkman, 1984) to help with questionnaire development, and two measures used in this study were based on the model. These assessed the stress caused by and confidence in cognitive appraisals about BRCA1/2 pathogenic variants. Another study (7%) utilized the Theory of Planned Behavior to inform the development of a questionnaire used in the study. It is perhaps important to note that this information was not published in either of these papers, and rather was presented in separate published protocols detailing methodology (Halbert et al., 2004; Kiechle et al., 2016). There was limited evidence of explicitly linking this theory to intervention techniques, or for use in tailoring the intervention design in either publication.

Overall, there was limited mention on the use of theory to develop these interventions. Five studies (33%) mentioned a theoretical aspect of intervention design, of which three (20%) employed a middle-range theory only. The implicit assumption, however, within these interventions can be understood as follows: education and/or peers can provide informative content and support, through which individuals can learn how to cope better with psychological concerns. This is achieved by tackling misinformation regarding perceived risks, and improving knowledge surrounding the implications of a BRCA1/2 pathogenic variant, while providing aspects of social support and the benefit of sharing of mutual experiences.

### 3.9 Public and patient involvement

It was agreed that relevant charities and patient groups should be approached to distribute study findings. This was considered
important to ensure that sources providing such information are reliable, trustworthy, and objective.

Specific details of interventions were deemed of interest to the PPI panel. For example, PPI members relayed that knowing details regarding demographics of the participants in the included intervention studies would be relevant to disseminate, most specifically around the stage of preventative measures/screenings. Specifically, information regarding whether participants had undergone prophylactic surgeries, and if so which types, or if participants were opting for screening only was considered of key interest. However, it was discussed that such information can sometimes be overwhelming and lead to information overload, and therefore, it is important to ensure that findings are accessible and concise.

In regard to accessibility, the issue of terminology and language was raised as an issue by both the PPI panel and the once-off ‘Dragon’s Den’ consultation. The term ‘alteration’ over ‘pathogenic variant’ or ‘mutation’ will be utilized during lay-person dissemination of the current study findings. The term mutation is to be avoided as it was said to bring up thoughts of being a ‘mutant’. Similarly, ‘patient’, and ‘diagnosis’ will not be utilized, as with it come negative connotations of an illness diagnosis, whereas the identification of a BRCA1/2 pathogenic variant does not always coincide with a cancer, and individuals in this cohort may equally experience psychological distress.

4 | DISCUSSION

In this systematic review of 15 interventions utilizing different approaches to address psychological outcomes in women with a BRCA1/2 pathogenic variant, a minority of the studies had some long-term effect on the psychological outcomes of participants. A number of those interventions that revealed significant results were often those that utilized decision aids, or were conducted in a group setting. The main parallel noted across studies was an emphasis on the educating of participants on topics pertinent to the BRCA1/2 population, but the method through which this was operationalized differed among the interventions. The lack of high-quality interventions, designed with attention to relevant theories indicates a dearth of adequately conducted research in this population. A key finding from this systematic review is that more rigorous interventions should be designed, with consultation with the BRCA1/2 population and key outcomes agreed upon. This echoes the recommendations of a prior review in the topic area (Jeffers et al., 2017), highlighting the necessity for further investigation in the field. As we move into a more personalized medical approach, wherein genetic screening is more widespread among our general population, a fundamental need becomes clear – ensuring that future research is relevant to the population at hand, and more successful in improving upon psychological outcomes for BRCA1/2 pathogenic variant carriers.

4.1 | Use of theory

There was limited use of theory in the interventions assessed. A middle-range theory, classified as a theory that is a combination of empirical evidence and theoretical and conceptual components, was employed in three of the 15 studies. Only one pure theory was mentioned throughout the included interventions, in which it was employed to assist with the development of two measures, with no input mentioned elsewhere in the study. This is a limitation within the literature, given that theory-based designs are beneficial to aid replicability of approach, and it is suggested that theory-driven interventions can have a stronger impact on a given population. For example, a recent systematic review assessing the influence of physical activity interventions in populations of breast cancer survivors posited that the more extensive the use of theory in the design, the more enhanced the effectiveness of these interventions (Bluethmann et al., 2017).

4.2 | Other hereditary cancer populations

As genetic testing becomes more widespread, a larger BRCA1/2 pathogenic variant population is expected to be identified in the near future. With recent discoveries in the cancer genetics field highlighting more pathogenic variants associated with heightened breast cancer risk (Narod, 2021), it is paramount that researchers and stakeholders preempt the surge in demand for psychological care. It is, therefore, vital that intervention research in the area is validated in other hereditary cancer populations by adapting pre-existing interventions and supports, rather than investing time and resources into creating new interventions. With regard to the BRCA1/2 pathogenic variant population, it is likely that other conditions which effect hereditary breast and gynecological cancer risk can benefit from such psychological research. These cohorts may include individuals with Lynch Syndrome, linked to gynecological cancer risk (Toss et al., 2015), or those with pathogenic variants such CHEK2, PALB2, and TP53, suspected to cause a moderate to high increased lifetime breast and ovarian cancer risk (Narod, 2021; Toss et al., 2015). As such, it may be feasible for the findings of studies included in this review to be adapted to these cohorts, ensuring timeliness of research for these populations and improving availability of psycho-oncological supports for hereditary cancer populations.

4.3 | Racial disparities

There was minimal reporting of race/ethnicity of individuals in the study populations, with only three (20%) papers presenting such data. This issue is heightened with only one (7%) study documenting if individuals were of Ashkenazi Jewish heritage (central and eastern European), a demographic known to be at high risk of carrying a BRCA1/2 pathogenic variant (Tang et al., 2017). A recent publication notes that pathogenic variant prevalence in Black
populations is similar to that of Ashkenazi Jewish populations (Ciuro et al., 2020). Racial disparities are prevalent in the identification of such pathogenic variants, with minority groups such as Black women often omitted from genetic testing referrals (Cragun et al., 2017). Multiple factors indicate the pressing need for referral in the Black population, such as higher incidence rates of triple-negative breast cancer at a younger age (Jones et al., 2017). Cancer-specific distress and clinical depression have been noted in Black women at high risk of carrying a BRCA1/2 pathogenic variant (Cukier et al., 2013), and this distress trajectory occurs in a different pattern to that of other individuals in other racial/ethnic groups (Hamilton et al., 2009).

This is a well-documented issue within the field of cancer research at large, with severe disparities reported in the participation of clinical trials in the United States (Regnante et al., 2019) and a lack of reporting of race/ethnicity in individuals participating in clinical trials (Loree et al., 2019). This issue is furthered by noted barriers for those of African-American descent to participate in such research (Rivers et al., 2013). It can be therefore assumed that if not explicitly reported, the majority of participants in the included studies were white non-Hispanic individuals. As a guideline, researchers should aim to match the demographics of participants to population percentages in the country of study origin (Woods-Burnham et al., 2021).

4.4 | The use of PPI

Inclusion of PPI ensures the relevancy of research for the target group. The current review made use of PPI and recommends this for future research. The inclusion of a PPI panel in a systematic review was a novel component which strengthened this review. The input from this panel will increase the likelihood of the BRCA1/2 pathogenic variant population engaging with the findings from this review. For future evidence synthesis, the inclusion of a PPI panel earlier in the development and design process would further ensure that review outcomes remain relevant to the target population. For example, incorporating PPI input in developing inclusion and exclusion criteria would be of benefit. Future research should incorporate the inclusion of PPI panels in both original research and evidence synthesis. Incorporating service providers (e.g., genetic counselors) in the PPI process would also be of value and will further ensure relevancy of research for clinical practice.

4.5 | Future interventions

The development of future interventions targeting BRCA1/2 pathogenic variant carriers should ensure stakeholder involvement. While no single intervention design was deemed superior to another due to the heterogeneity of the included studies, it is evident that educational strategies are a worthy prospect for future investigation. Psycho-educational interventions should focus upon teaching strategies for coping with stress specific to BRCA1/2 related issues. This could include increasing knowledge about risk perceptions, to ensure that individuals do not have a heightened sense of their own lifetime cancer risk, and provision of skills to enable communication about this risk in families. Interventions in this review that utilized such methods were successful at decreasing cancer-specific distress at certain time points. Telephone counseling also reduced anxiety levels, and so this type of intervention merits further attention. It may be feasible to conduct such research utilizing social media, such as Facebook, wherein closed groups for BRCA1/2 pathogenic variant populations are pre-established and their relevance to peer support has been already documented (Stefansdottir, 2016).

The Ottawa Decision Support Framework (O’Connor et al., 1999), a middle-range theory, designed within the context of Decision Aids for the BRCA1/2 pathogenic variant population, holds merit for further research. Alternatively, a recent study which focused on improving communication between patients and genetic counselors, employed the Theoretical Domains Framework (Cane et al., 2012), and the Behavior Change Taxonomy Technique (Michie et al., 2013). These theories are considered reliable and robust when designing interventions aimed at changing behavior, and could inform future interventions for those with hereditary cancer conditions. While there are numerous studies within the field of cancer genetics using these theories, they tend to target healthcare professionals in the area, rather than patient groups. Greater understanding of the needs of the BRCA1/2 pathogenic variant population will be of value to health professionals, such as genetic counselors, and will assist with referral to appropriate psychological support services.

4.6 | Limitations

No preprint servers were screened for relevant texts, which may have held gray literature relevant for this review. Furthermore, the Association of Genetic Nurse Counselors do not currently provide online access to conference abstracts, and so hand-searching of these conference presentations was not possible, as originally intended. This is unlikely to have identified any further studies as searching another similar set of conference abstracts did not yield any relevant results.

5 | CONCLUSION

This systematic review was the first to address the efficacy of interventions for the BRCA1/2 pathogenic variant population at large and extends the limited evidence synthesis conducted in this field to date. The studies included in this review were heterogeneous in approach and design. The review found limited studies at low risk for bias, with few studies making use of theory or adequately utilizing it throughout the entire design process. Findings thus indicate a need...
for more robustly designed interventions, incorporating the use of relevant theory.

This review further highlights the lack of diversity in study populations, the need for patient, public, and stakeholder inclusion in intervention design, and the need for future research to advance interventions into other hereditary cancer cohorts. The inclusion of individuals with a BRCA1/2 pathogenic variant from different racial/ethnic groups in intervention research warrants immediate attention.

It is paramount that adequate psychological supports are developed and made available to this growing cohort. Notwithstanding the methodological limitations identified, this review highlighted the type of interventions that alleviated anxiety, cancer, and genetic-specific distress in individuals with a BRCA1/2 pathogenic variant.

**AUTHOR CONTRIBUTIONS**

As per the criteria set by the International Committee of Medical Journal Editors (ICJME), NW and AMG provided substantial contributions to the conception and design of the work; and all authors provided substantial contributions to the acquisition, analysis, and interpretation of the data for the work; worked on drafting and revising this work; gave final approval of this version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**COMPLIANCE WITH ETHICAL STANDARDS**

**CONFLICT OF INTEREST**

NW, AMG, JMS, and SM declare that they have no conflict of interest. This research was supported by National University of Ireland, Galway Doctoral Scholarship, and Irish Research Council Funding, both awarded to NW.

**HUMAN STUDIES AND INFORMED CONSENT**

No human studies were conducted for this research.

**ANIMAL STUDIES**

No non-human animal studies were carried out by the authors for this article.

**DATA SHARING AND DATA ACCESSIBILITY**

The data that supports the findings of this study are available in the supplementary material of this article. Further data that support the findings of this study are available in Open Science Framework at doi.org/10.17605/OSF.IO/P34KT.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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