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Review Article

The changing health of Thalidomide survivors as they age: A scoping review

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abstract

Background: In the late 1950s and early 1960s the drug Thalidomide was given to thousands of pregnant women across the world to relieve morning sickness. The drug caused severe birth defects. Much has been written about the drug, its teratogenic effects, and the nature of the damage it caused. There is however, little literature exploring ageing with Thalidomide damage.

Objectives: The aim of the review was to bring together, for the first time, the evidence about the Thalidomide-related health problems Thalidomide survivors are experiencing, as they grow older. Methods: A systematised review of published and grey literature, in which grounded theory provided a heuristic for the evidence synthesis.

Results: Twenty-five relevant papers were found. They included biomedical papers focusing on specific health problems, alongside surveys and mixed method accounts exploring the health of Thalidomide survivors. Most studies had physical health as their primary focus.

Conclusions: The two most frequently reported groups of health problems were musculoskeletal and mental health conditions. There was little discussion about the social consequences of secondary damage being layered onto lifelong impairments or of the implications of co-morbidities. Future research needs a stronger connection to more social models of disability and critical disability studies.

In the late 1950s and early 1960s the drug Thalidomide was given to thousands of pregnant women across the world to relieve morning sickness. The drug caused severe birth defects, which are referred to as Thalidomide Embryopathy or Thalidomide Syndrome. Thalidomide survivors were born with a range of impairments.[1] Most commonly they have missing or short and/or deformed limbs (Phocomelia). Some people have sight or hearing impairments and/or facial disfigurement. A few have brain damage. Thalidomide damage can also be unseen, affecting internal organs. Globally, thousands of Thalidomide survivors and their families continue to live with the medical and social consequences of Thalidomide. As they age, they are experiencing new Thalidomiderelated health problems, as well as deterioration in their original impairments. This can lead to disabling and discriminatory outcomes, of which we know relatively little.

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Much was written in the 1960's and 1970's about the drug Thalidomide, its teratogenic effects, and the nature of the damage it caused.[2,3] During the 1980 and 1990s there were a small number of studies involving younger adult Thalidomide survivors but these tended to focus on narrow topics (e.g. the ophthalmic consequences of Thalidomide[4]). Only in the 2000's, when Thalidomide approached its 50th 'anniversary' and Thalidomide survivors entered middle age, did research about the health of Thalidomide survivors as adults began to appear in academic journals. Since then several reports and papers have been published. Some focus on early onset health problems. Others look more broadly at health and quality of life. There are however, no published reviews about ageing with Thalidomide damage. A few studies briefly examine the literature but this is restricted to an area of clinical interest. Consequently, the current literature fails to reflect both the complexity of the health problems many Thalidomide survivors face, and the broader social context.

This paper presents the results of a conventional scoping review[5] of published and grey literature (documents produced by governments, charities or businesses, which are not commercially published) about Thalidomide-related health problems survivors are experiencing, as they grow older. The review also encompassed the literature on health-related quality of life but this is the subject of a separate paper.

Methods

A protocol was developed[6] to ensure that the review included as many elements of the systematic review process as possible. However, resource constraints (e.g. one reviewer), the heterogeneous nature of the literature, the high proportion of grey literature and the variation in the quality of the studies, meant that a fully systematic review was not possible. The review was part of a doctoral study which drew on grounded theory methods. These

provided a heuristic for the evidence synthesis. To facilitate quality control, EN discussed decision making with KA.

Search strategy

An initial exploratory search of MEDLINE was undertaken to gain a better understanding of the nature of the literature and to inform the development of the search terms to be used in the electronic searches. Seven electronic databases were searched MEDLINE (1946 Onwards) (OvidSP), EMBASE (OvidSP), CINAHL Plus (EBSCO), PsychINFO (OvidSP), ASSIA (ProQuest), Social Policy and Practice, and Index to Theses. The search strategies for each database used both subject headings and key words. The search was run in May 2015 and up-dated in November 2016. Four new papers were found. The search strategy used for MEDLINE is shown below in Table 1 as an example.

The exploratory search, suggested that there would be not more than 30 to 40 relevant studies published in peer reviewed journals. Furthermore, we were aware that several relevant studies took the form of reports, which were in the public domain but did not appear in the published academic literature. For this reason it was necessary to supplement the searches of electronic databases with four other approaches:

Searching websites of Thalidomide organisations

Contacting experts in the field through the UK Thalidomide Trust and the European Dysmelia Reference Information Centre 'Hand' searching reference lists and journals

Google Searches using a number of different words and phrases

Screening, selection and quality appraisal

Two broad eligibility criteria were used for initial screening of the records - studies were only included if they were concerned with exposure to Thalidomide whilst in the womb; and focused on people born with physical and/or mental impairments that resulted from their mothers taking the drug during pregnancy. Given the considerable variation in the size of studies, study designs and contexts, no restriction was placed on the type of study to be included. The full text of all potentially relevant papers was then assessed using four questions:

Is the study population Thalidomide survivors born in the late 1950 or 1960's?

Does the study report on the health and/or impairment of Thalidomide survivors?

Does the study report on the health-related quality of life of Thalidomide survivors?

Does the study focus on the health/quality of life of Thalidomide survivors in middle age?

If the answer to the first question and at least one of the following questions was 'yes' we included the study. We decided not to exclude studies which made no explicit reference to ageing as some biomedical studies, whilst being condition focused could include implicit references to ageing. A study selection form was developed to document decisions. Details of the literature flow are given in Fig. 1.

The issue of quality assessment created some challenges. The quality of the studies varied significantly but we decided not to exclude any studies at the study selection stage on the grounds of quality, as even studies of a lower quality might yield some useful insights (and this did prove to be the case). However, during the data extraction stage, we did make a basic assessment of the quality of the studies and our comments are included as part of our analysis. Due to the diverse nature of the studies, we did not use any standard quality appraisal tools. However, we drew on three sources[6,7,8] to devise a simple appraisal framework which we used to note the quality of the: study design; analysis and findings; reporting; and contribution to knowledge and understanding. These notes influenced the weight placed on the findings from some studies, especially where they were not supported by data from other studies. In this way, they informed the literature synthesis.

Data extraction and synthesis

A data extraction form was completed for all the included papers, focusing on the aims of study; setting; theoretical background; sampling approach; participants characteristics; design (data collection & analysis); and findings. The data was extracted by the lead author (EN) and a sample of data extraction forms was reviewed by the second author (KA).

Grounded theory provided a heuristic for the evidence synthesis.[9] Previous work by Kearney[10] and Bailey et al.[11] informed our approach, which had two main elements. Constant comparative analysis enabled us to: analyse the data descriptively; identify categories that cut across the studies; compare data from different types of studies; move between and bring together findings from studies that were very different in scale and scope; and 'convert' quantitative data from the studies in to narrative description. We then used initial coding to identify key themes from across studies.

Table 1
Search Strategy use for MEDLINE.

#1	thalidomide OR distaval OR tensival OR asmaval OR valgis OR valgraine OR sedoval OR celgene OR contergan
#2	Pregnan$ OR during adj3 pregnancy OR in adj3 pregnancy
#3	#1 AND #2
#4	Impair$ OR damage$ OR disable$ OR disabilit$ OR handicap$ OR deformit$ OR deform$ OR affect$ OR consequen$ of
#5	#3 AND #4
#6	health OR health problem$ OR physical health OR mental health OR illness$
#7	#5 AND #6
#8	#3 AND #4 AND #6

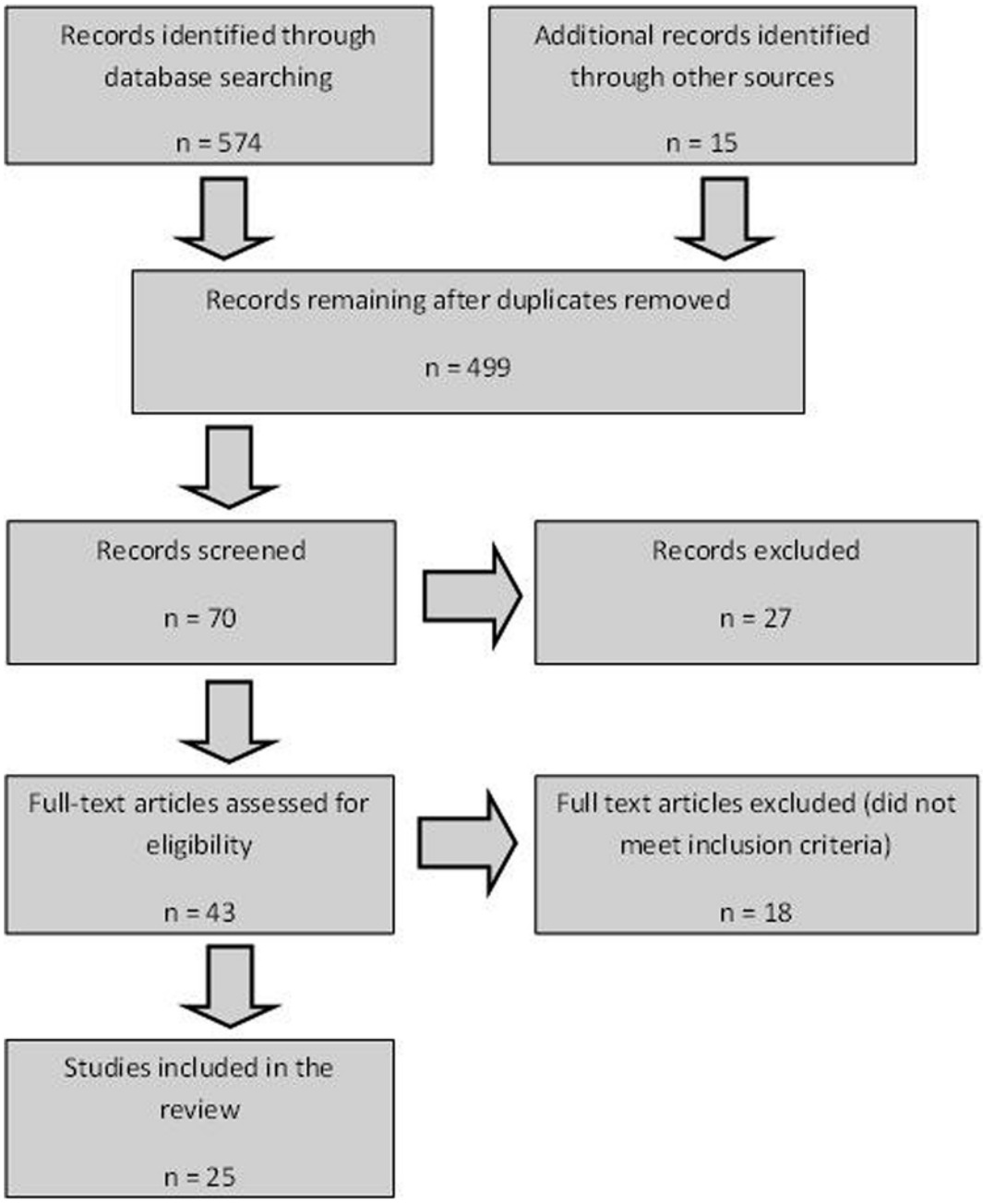

Fig. 1. Flow Diagram of the Literature Review Stages.

The codes were developed by EN and then refined through discussion with KA.

Results

The studies in the review included quantitative, qualitative and mixed methods studies, with a high proportion of grey literature. Appendix A presents an overview of the 25 included papers in relation to: focus and aims; population and sample size; and methodology, methods of data collection and analysis. Thalidomide was distributed in 47 countries but the studies came from just seven countries where there are significant numbers of Thalidomide survivors e Australia, Canada, Germany, Ireland, Japan, Sweden and the UK. They included biomedical papers focusing on specific health problems, accounts of surveys exploring the health and health related quality of life of Thalidomide survivors, and multi-methods studies; most of which took the form of reports for government bodies or organisation representing Thalidomide survivors. Most studies focused on physical health, and in the biomedical papers, musculoskeletal problems were the most commonly researched topic.

Primarily the literature documented the on-set of health problems in middle age. Several studies discussed ageing with the lifelong impairments caused by Thalidomide. However, few explored the experience of living with lifelong impairments and the impact of secondary health problems. Few papers made a connection to disability theory and we consider the implications of this further in our discussion.

Musculoskeletal problems

Fourteen studies discussed the musculoskeletal problems. These discussions ranged from accounts of the problems being reported by Thalidomide survivors in qualitative interviews and health surveys to biomedical studies focusing on specific conditions.

In Kennelly et al.'s 2002 study,[12] UK Thalidomide survivors who were entering their 40s, reported musculoskeletal problems. Around 20% of the respondents to their survey of all UK Thalidomide survivors said they had arthritis, with similar proportions reporting 'increased joint pain' and 'increased muscular pain'.[12]

A decade later, an evaluation of a government Health Grant to UK Thalidomide[13] survivors (n ¼ 60) found that over three quarters were experiencing deterioration in one or more joints, and joint, back and/or neck pain. For many participants, these musculoskeletal problems were associated with over-use of 'good' limbs or the ways in which they had to use their bodies to compensate for their impairments. A Japanese study of the health of 201 Thalidomide survivors[14] describes musculoskeletal problems as 'overuse syndrome'. The paper also included some limited data about prevalence with around a third of participants reporting joint pain and a similar proportion shoulder stiffness.

In both the UK studies, Thalidomide survivors were beginning to feel that their health - and particularly their musculoskeletal health - was not as good as their non-disabled peers. However, this theme emerged with more clarity in the second report from the Health Grant evaluation,[15] with some participants stating that they felt older than their chronological age - "I feel like I have the body of a 70 year old".

Four studies reporting on the health and quality of life of Thalidomide survivors also presented findings about musculoskeletal problems. Nippert[16] explored the health related quality of life of 104 female Thalidomide survivors in Germany found that 41.6% of the survey respondents described experiencing deterioration in their health in the preceding twelve months. Of this group, 83% reported increased musculoskeletal problems. Bent et al.[17] found that almost half the 41 UK Thalidomide survivors who responded to their survey reported having arthritis in their shoulders and just over a third reported hip pain. Thalidomide survivors with more severe impairments reported significantly more musculoskeletal problems. O'Carroll et al.[18] also note that the Thalidomide survivors in Ireland reported deterioration in their 'original condition' ... due to hand and arm overuse, injuries and musculoskeletal problems affecting the feet, knees and back'. Finally, in the Thalidomide Victims Association of Canada (TVAC) survey[19] 80% reported increasing muscular pain and 71% reported increasing joint pain.

There have been two large German studies into the health and socio-economic circumstances of Thalidomide survivors as they age. The Contergan Foundation for People with Disabilities commissioned the first[20] and asked the University of Heidelberg to 'identify the existing care deficiencies and future special needs of thalidomide victims'. Material from 870 Thalidomide survivors from across Germany was collected via surveys, face-to-face interviews and focus groups. The study described 'secondary damages', which the authors defined as: "physical impairments that develop in thalidomide victims during the course of their lives in areas of the body not damaged prenatally",' caused by "some movement patterns practiced early on to compensate for missing functions" (p14). The authors distinguish these 'secondary damages' from 'long term sequelae' (i.e. prenatal damage detected at a later point).

The survey questionnaire asked respondents to indicate the severity of four musculoskeletal problems e pain, osteoarthritis, muscle weakness and muscle tension e using a simple four point scale. The results were compared to a similar survey conducted by the authors five years earlier. The study found that musculoskeletal problems in the 'upper extremities' were significantly worse than five years earlier. There was also deterioration in the 'lower extremities' and 'vertebral column/pelvis'. Severity of pain, osteoarthritis, muscle weakness and muscle tension in the 'upper extremities' were clearly associated with the severity of original Thalidomide damage; but for the 'lower extremities' and 'vertebral column/pelvis' the picture was less clear. A linked survey of participants' physicians found that 90% of the problems presented during consultations "related to the musculoskeletal system".

The University of Heidelberg study[20] also discussed the pain associated with musculoskeletal problems. They found that 84.3% of their survey respondents experienced pain. Of this group, 50% experienced pain 'every day' and 39% had 'persistent' pain. The proportion of respondents reporting pain increased with the number of 'damage areas' they had. The authors suggested:

"The reason for pain is both wear and tear, or destruction of damaged joints, as well as tension in muscle attachments and tendon insertions. Pain is also the result of secondary damages that have developed in area not affected prenatally. In practice, it is quite difficult to separate the two causes of pain and functional impairment. The current situation defines the everyday life of the victims and represents the situation that has shaped itself in the amalgamation and development of prenatal damages and secondary damages over the course of 50 years." (p16).

The second German study,[21] was a multi-methods study of the 'Damage to Health, Psychosocial Disorders and Care Requirements of Thalidomide Victims' in North Rhine Westphalia. It involved face-toface assessments, clinical examinations and diagnostic tests. A selfselected but representative sample of 202 Thalidomide survivors took part. Two doctors examined each participant and then completed a questionnaire, which recorded both 'primary impairment' (i.e. original Thalidomide damage) and 'consequential damage'. For consequential damage, data was collected about loss of movement and musculoskeletal pain in joints/areas of the body. Pain was most frequently reported in the neck, back and shoulders, closely followed by knees and hips. Movement restrictions were most common in the hand, shoulder and elbow, and around two thirds of participants had painful, hypertonic muscles in one or more area of the body. In the self-completion questionnaire 27.7% of respondents listed diseases of the musculoskeletal system and connective tissue.

Finally, three papers examined specific musculoskeletal problems. An early case study by Newman[22] described a shoulder joint replacement procedure for a then 35-year-old Thalidomide survivor with end-stage osteoarthritis. Although a single case study, it highlighted three important issues: the likelihood of Thalidomide survivors developing degenerative joint disease, which compound existing impairments; the need to recognise 'overuse symptoms'; and the potential benefits of shoulder replacement. More recently, a Swedish study by Ghassemi Jahani et al.,[23] examined the development of osteoarthritis in the 'lower extremities' of 26 Thalidomide survivors using computed tomography scans and the Rheumatoid and Arthritis Outcome Score. The authors found that nearly 40% of the participants had osteoarthritis in the hip and 60% in the knee. They conclude that for these conditions, the prevalence rates found in Thalidomide survivors are higher than in the general population of a similar age but suggest that these degenerative changes "were mostly mild and had little clinical significance".

A second paper by the same lead author[24] examined degenerative changes in the cervical spine in a group of 27 Swedish Thalidomide survivors; and compared them to 27 age and gender matched controls. They found that Thalidomide survivors had a significantly higher degree of disc degeneration alongside other changes, notably foraminal narrowing (i.e. narrowing of the passageway through which all spinal nerve roots pass). They concluded that Thalidomide survivors have a higher frequency of degenerative changes in the cervical spine and suggest that this may be caused by an altered load on the cervical spine. In addition, a case study of one Canadian Thalidomide survivor[25] highlighted the impact of back and neck pain on daily life.

Pain and neuropathic symptoms

Whilst muscle and joint pain associated with musculoskeletal problems were common, three studies[15,19,20] also found that some Thalidomide survivors reported generalised, possibly neuropathic pain and neuropathic symptoms such as numbness, tingling, loss of sensitivity/dexterity and partial paralysis. None of these studies, however, makes comparisons with pain prevalence in the general population of a similar age.

Only one study - Peters et al.[21] specifically examined the issue of neuropathic pain. They used the painDETECT questionnaire and found that around 20% of participants probably had a neuropathic component to their pain, compared to an estimate of 8% in the general population in Germany aged 45e54.[26] Participants without Dysmelia were most likely to have a neuropathic pain component. Two other studies looked at late-onset neurological symptoms. The first by Jankelowitz et al.[27] involved 16 Thalidomide survivors from Australia and New Zealand who had all presented with new neurological symptoms. The aim was to "determine whether there was ongoing nerve damage/loss in this population as a 'late effect' of thalidomide exposure or whether the effects were due to exacerbation of the normal ageing process as a result of lack of the normal 'redundancy' within the nervous system" (p509). The study involved taking detailed medical histories, clinical neurological examinations and neurophysiological testing. The authors found no evidence of clinically or neurophysiologically late-onset generalised neuropathy and concluded that the neurological symptoms experienced by their participants were largely due to compressive neuropathies.

The second paper[28] reported on a pilot study designed to determine whether UK Thalidomide survivors had problems with their peripheral nerves. The 17 Thalidomide survivors involved all reported sensory symptoms in their upper limbs and a few in their feet. They took part in a range of motor and sensory examinations and their results were compared to 17 healthy volunteers. The authors found that the majority of the Thalidomide survivors in the study (15 out of 17) had nerve compression, most commonly around the wrist but also of the nerve roots in the lower back and of the spinal cord in the neck. The findings for generalised neuropathy were less clear. They suggest that some symptoms could be due to abnormal peripheral nerve development or (in the lower limbs) early peripheral nerve dysfunction but that more research is needed.

Jankelowitz et al.[27] also noted that the chance of developing median nerve compression at the wrist was probably greater in Thalidomide survivors because overuse of the hand to compensate for other limb deformities coupled with musculoskeletal deformities may lead to narrowing of the carpal tunnel. A small study[29] of three Japanese Thalidomide survivors with Carpal Tunnel Syndrome and radial dysplasia (i.e. absent or underdeveloped radius bone in the forearm) supported this finding, as did Kayamori's 2013 study.[14]

Dental problems/facial damage

Just one study looked specifically at the dental health of Thalidomide survivors. Ekfeldt and Carlsson[30] examined the dental status and oral function of 31 Swedish Thalidomide survivors. They found that dental caries was similar to general population but the number of decayed, missing or filled teeth was slightly higher. They suggest that this might be because Thalidomide survivors find tooth brushing more difficult. They also found that tooth wear was on average more extensive than the comparable age group in the general population. The authors suggested this could be due to dental erosion associated with high prevalence of regurgitation amongst Thalidomide survivors and to a lesser extent by using teeth as tools.

The findings from Newbronner et al.[15] and those of Kruse et al.,[20] support Ekfeldt and Carlsson's[30] findings. Upper limb affected participants frequently used their teeth to help them with everyday tasks such as getting dressed, opening bottles and holding keys. Participants also described having difficulty cleaning their teeth properly, which could lead to higher rates of tooth decay.

Peters et al.[21] also found that a third of participants reported tooth wear and this was significantly more common amongst participants with Dysmelia. A study linked to Ekfeldt and Carlsson's,[30] which involved 25 of the same participants, surveyed the frequency and characteristics of facial palsy in Thalidomide survivors.[31] They found that three (10%) had acquired facial palsy - more than would occur by chance - and suggest this may indicate that the facial nerve in Thalidomide survivors is more vulnerable.

Deteriorating sight and/or hearing

In the UK, around a quarter of Thalidomide survivors were born with damage to their eyes and almost a third have a hearing impairment. The first study to highlight concerns about deterioration in middle-age was Nippert's study[16] of female Thalidomide survivors, with 13% of survey respondents reporting ear and eye problems. In 2011 Newbronner et al.[13] noted that the Thalidomide survivors in their study who were partially sighted and/or partially deaf were reporting further deterioration in their sight and/or hearing. The TVAC survey[19] found that around 22% of respondents reported 'deterioration in eyesight' and around 15% 'deterioration in hearing'. However, it is not clear what proportion of these respondents are Thalidomide survivors who had original damage to their sight or hearing. Further, no comparisons with age matched population norms were made.

General health

One study, conducted in Japan, looked specifically at 'lifestyle diseases'.[32] The study found that the most common lifestylerelated disease amongst Thalidomide survivors was hypertension, which affected nearly half the 76 participants, followed by obesity, which affected nearly a quarter of participants. The paper made few direct comparisons with the general population of a similar age but it did highlight gender differences, noting that male Thalidomide survivors were at higher risk of developing lifestyle related diseases. Importantly, the authors' reflected on the problem of accurately measuring blood pressure and body mass index when people have missing or short limbs. These are two of the most commonly used indicators of risk of lifestyle diseases, and yet Thalidomide survivors may be less able to benefit from them because of the unreliability of the measurements produced. Taking accurate blood pressure reading for people with limb difference is difficult. A standard cuff may be unsuitable or it may have to be placed on the leg which produces a less reliable reading. The use of general population norm when interpreting results also raises questions of validity. Newbronner et al.[15] also briefly discuss the complications of managing lifestyle related conditions such as diabetes and hypertension.

A second Japanese study[33] examined the prevalence of "internal anomalies in Thalidomide embryopathy" in 22 "selected" participants using MRI and CT imaging. The study found a high prevalence of abnormalities of the inner ear, the vascular system and the gallbladder (which may have implications for general health). The paper concludes by noting the value of using MRI and CT imaging to identify internal abnormalities but unfortunately says nothing about the implications of these abnormalities for the health of Thalidomide survivors.

Mental health

Five studies explored the mental health of Thalidomide survivors. Of these, just two specifically set out to assess the prevalence of mental disorders. Imai et al.[34] examined the psychological and mental health problems of 22 Japanese Thalidomide survivors and compared them to a 'healthy' control group. The participants in this study (nine men and thirteen women) had been admitted to hospital for general medical examinations. Whilst their original Thalidomide impairments were briefly described, no information was provided about how representative they were of the population of Thalidomide survivors in Japan.

The General Health Questionnaire-28 (GHQ-28) was used to measure psychological distress and minor psychiatric disorders. Fifty-nine per cent (13 out of 22) were judged to have some kind of mental health problem. The average GHQ score for the Thalidomide survivors (7.36; SD 5.34) was significantly higher than the 'healthy' subjects group (2.76; SD2.31; P 0.01). Imai et al. also found that participants who were single or divorced had higher depression scores and higher scores for impaired social activity than married participants. However, the study did not comment on how this

compared to the 'healthy' subjects. The authors also used MINI, a short structured psychiatric diagnostic interview instrument, to make diagnoses of psychiatric disorders. They found that 40.9% of participants had one or more psychiatric disorders but no comparison with the general population in Japan was made.

Peters et al.[21,35] assessed the prevalence of what they described as 'psychological co-morbidities' using a structured clinical interview for DSM-IV diagnosis and a clinical psycho-diagnostic interview. They obtained results for 95.6% (n ¼ 193) of their study participants:

- 47.2% of participants had a point or 4-week prevalence of at least one mental disorder compared to a 12 month prevalence in the German general population aged 50 to 64 of 27.1%
- Male Thalidomide survivors were more likely to experience mental disorder than their female peers, which is in contrast to the general German population
- The four most frequent diagnostic groups were: depressive disorders (23.8%); somatoform disorders (18.1%); anxiety disorders (16%); and substance misuse (9.3%).
- For the two most frequently diagnosed disorders (depressive and somatoform), prevalence was higher amongst participants with no Dysmelia. However, it is important to note that almost two thirds of the no Dysmelia group were deaf or had a severe hearing impairment and many also has facial damage

The authors concluded that Thalidomide-survivors were more likely to be affected by mental disorder than the general German population, and that the lifetime prevalence of depressive disorders was more than double that in the general population.

In their survey of 870 German Thalidomide survivors, Kruse et al.[20] looked specifically at the prevalence of depressive disorders, using the Major Depression Inventory (MDI), a self-report mood questionnaire. They estimated that 11.7% of their survey respondents were suffering from a depressive disorder, compared to 8.1% of the general German population aged 50 to 65. Like Peters et al.[21] they also found that in contrast to the general population, there was no substantial difference in prevalence between male and female Thalidomide survivors. They did, however, identify a number of factors that appeared to increase the risk of Thalidomide survivors experiencing depression, including: a poor social network; unemployment; recent experience of severe pain; the need for long term care and assistance; and the severity or extent of participants' Thalidomide-impairments (i.e. the number of limbs affected; sensory impairments; internal organs damaged etc.).

In addition to the three studies described above, the TVAC survey[19] found that, in the past five years, 23% (15 out of 65) of respondents reported experiencing depression. Kennelly et al.[12] also found increasing experiences of depression linked to the effects of living with physical impairments.

Discussion

The literature about the health of Thalidomide survivors as they age is not extensive. It is not of the highest level of scientific rigour and many of the biomedical studies have a narrow focus on specific conditions or pathologies. As such, there are parallels with the literature on ageing with cerebral palsy, where it took two decades to develop the evidence about functional decline associated with ageing.[36,37] Nevertheless, the studies in this review make an important contribution to an under researched area and together they do present a picture of the secondary damage people are now experiencing. Table 2 below synthesises the evidence using initial grounded theory coding.

In particular the literature suggests that the two most common groups of health problems are musculoskeletal conditions and mental health problems. The prevalence of musculoskeletal conditions highlights the question of whether Thalidomide Survivors, like other people with early onset disability, should no longer be encouraged to continually maximise function but rather "conserve it and preserve it".[38,39]. More broadly it suggests that whilst conditions like Thalidomide embryopathy and other birth defects are non-progressive, the consequences of them are not static, and so greater emphasis needs to be places on people managing their bodies across the life course.[40]

The apparently high proportion of Thalidomide survivors who are experienced depression and anxiety confirms the known link between disability and poor mental health.[41] More particularly it suggests that the additional loss of function (especially difficulties with activities of daily living) caused by secondary damage, may increasingly be placing Thalidomide survivors at greater risk of mental health problems.[42]

However, the biomedical literature only presents a partial picture. More extensive inclusion of comparative data of the health of the general population, and the use of assessment tools more sensitive to the experience of early on-set

Table 2
Initial grounded theory codes.

Descriptive Analysis Theme	Initial Grounded Theory Coding
Musculoskeletal Problems	Musculoskeletal problems are the most common health issue amongst Thalidomide survivors
	The prevalence and severity of musculoskeletal problems appears to increase with the severity of Thalidomide survivors impairments but this relationship is not simple or linear
	Secondary damage to joints and muscles is primarily caused by 'overuse' and postural adaptations
	The pain and movement restriction caused by secondary damage is compounding existing impairments
Pain and Neuropathic Symptoms	Neuropathic pain and symptoms are more common amongst Thalidomide survivors (including those with no Dysmelia) than the general population
	The causes of neuropathic pain and symptoms are disputed and often unclear
	Thalidomide survivors are more vulnerable to compressive neuropathies but these can be harder to diagnose and treat
Dental Problems/Facial Damage	Thalidomide survivors have higher levels of decayed, missing and filled teeth, and tooth wear than the general population
	The causes of poorer dental health are multiple, including difficulties with dental hygiene, using teeth as tools and regurgitation The dental and facial health of Thalidomide survivors is vulnerable
Deteriorating Sight and/or Hearing	Thalidomide survivors are reporting deteriorating sight and hearing
	It is unclear whether this deteriorating in sight and hearing is Thalidomide related or due to general aging
	There is very little evidence about the extent and nature of deteriorating sight and hearing, and the impact on Thalidomide survivors' quality of life
General Health	It is difficult to accurately measure blood pressure and body mass index when people have missing or short limbs and this can make affective treatment/prevention difficult
	Some Thalidomide survivors are aware that they are at risk of lifestyle related diseases but find their Thalidomide impairment make it difficult manage their weight or exercise
Mental Health	Hypertension may be more common amongst Thalidomide survivors but more evidence is needed
	Mental health problems appear to be more prevalent amongst Thalidomide survivors than the general population
	Depressive disorders are the most frequently diagnosed or reported mental health problem
	The relationship between mental health and severity of impairment is unclear but Thalidomide survivors with severe hearing impairment and facial damage appeared to be at greater risk of developing depression
	Other risk factors for poor mental health are similar to the general population and include poor social networks; living alone; unemployment; the need for on-going assistance; and recent experience of pain

disability, would strengthen the evidence base. The literature would also benefit from a discussion of the social consequences of secondary damage being layered onto lifelong impairments across the life-course; greater consideration of co-morbidities; and as Molton and Yorkston (2016)[43] propose, a more relevant and inclusive application of the "successful ageing" paradigm. It is the grey literature (i.e. the reports for Thalidomide organisations and state institutions) that provides most insight into the wider implications of the changing health of Thalidomide survivors and suggests a direction for future research. In particular, further research could benefit from a connection to more social models of disability (and critical disability studies),[44] particularly in articulating the broader disabling experience in which human rights come more to the fore.

Limitations

This review has three key limitations: there was only one main reviewer, although screening and study selection was discussed with the second author, who also reviewed a sample of data extraction forms and contributed to the GT coding; the quality appraisal of the included papers was limited; and the studies reviewed were of variable scientific rigour.

Conclusions

There is growing evidence that Thalidomide survivors are increasingly experiencing secondary health problems as they age, in particular musculoskeletal and mental health problems. However, the research is of variable quality and the discussion of the social consequences of additional health problems and further loss of function is limited. Even for Thalidomide survivors who have had some financial compensation, the social and economic impact of life changes resulting from impairment, can be considerable and the source of disadvantage, hence the need for a broader perspective in future research.

Conflict of interest

The authors have no conflicts of interest.

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Appendix A. Supplementary data

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