The impact of ageing on the health and wellbeing of people with thalidomide embryopathy: a comparison of the health impact with the general population

Katy Sagoe[1], W Andrew Owens[2], Rick Loyd[3], Rosemary Varley[4]

[1] Katy Sagoe, Director of Health & Wellbeing, Thalidomide Trust, St Neots, UK
[2] W Andrew Owens, 1. Professor, South Tees Hospitals NHS Foundation Trust, Marton Rd, Middlesbrough TS4 3BW, UK; 2. Biosciences Institute, Newcastle University, Newcastle upon Tyne, NE1 3BZ, UK; 3. Trustee, Thalidomide Trust
[3] Rick Loyd, CStat, Founder and Consultant at Change by Numbers Ltd, Ventnor, UK;
[4] Rosemary Varley, 1. Trustee, Thalidomide Trust; 2. Professor, Psychology & Language Sciences, University College London, London, UK.

Corresponding author: Katy Sagoe, Director of Health & Wellbeing, Thalidomide Trust

Contact details: katy.sagoe@thalidomidetrust.org; The Thalidomide Trust, Colmworth Business Park, Eaton Socon, Saint Neots PE19 8ER

ABSTRACT

Purpose: As people living with thalidomide embryopathy (TE) are now entering their seventh decade, we examine the impact of ageing and the prevalence of comorbid health conditions reported in holistic needs assessments (HNAs) by individuals with TE, compare it with an age-matched sample of the general population, and explore the relationship between comorbidities and TE pattern of impairment.
Materials and methods: The HNA categories were mapped and compared to those of the Health Survey for England (HSE) and analysed across four impairment groups (A-D).
Results: 94% (392/415) of individuals with TE residing in the UK participated in the HNA and consented to a secondary analysis of the data. Less than 2% (5/392) reported no comorbidities; 94% reported nervous system problems; including pain, pins and needles and numbness. Individuals with TE reported a significantly greater number of

health comorbidities, including musculoskeletal problems, than the age matched HSE population.

Conclusions: Individuals with TE report significantly more health and wellbeing concerns than the general population of a similar age. Long-term monitoring is needed to ensure that support and rehabilitation services can meet their evolving needs.

IMPLICATIONS FOR REHABILITATION

- People living with thalidomide's teratogenic effects are now entering their seventh decade.
- As they age, these individuals experience the long-term consequences linked to over-use of certain joints, including musculoskeletal and neuropathic pain.
- An understanding of the lived experience of TE with increasing age has the potential to inform the planning and provision of adequate and appropriate rehabilitation services moving forward.
- Adoption of a holistic approach to rehabilitation could help people living with TE to maintain functional independence as they enter their seventh decade.

KEYWORDS

Thalidomide; ageing; disability; rehabilitation; pain; loneliness

FUNDING

The author(s) reported there is no funding associated with the work featured in this article.

Introduction

The drug thalidomide was widely prescribed as a treatment for morning sickness during pregnancy between 1958 and 1961 in the UK [1]. Its successful use as a sedative and tranquiliser in the general population led to the perception that it was safe for use in pregnant women [2]. However, evidence of teratogenic effects when taken during the first trimester of pregnancy began to emerge [3,4]. These effects included severe damage to the developing foetus and became known as thalidomide embryopathy (TE) [1]. The extent and location of the resulting malformations varied according to the

frequency and the timing of thalidomide ingestion during embryonic development [5]. The most common and recognisable embryopathy was missing, shortened, or deformed limbs (phocomelia) [1]. Sight or hearing impairment and facial disfigurement also occurred [6,7]. Problems with reproductive or gastrointestinal systems were predominantly detected much later due to the limitations of diagnostic techniques at the time [8].

Globally, there are thought to be 3,000 to 4,000 thalidomide survivors [6]. They and their families continue to live with the medical and social consequences of exposure to the drug's teratogenic effects [6,9]. In addition, as they age, individuals with TE experience the long-term consequences linked to over-use of certain joints, leading to degenerative changes affecting the cervical spine and lower limbs [10,11], musculoskeletal pain and the early onset of arthritis [7,9,12]. Further studies describe eye problems [13], speech impairment [14], and problems with oral health [15]. In the UK specifically, a scoping review of thalidomide-related issues experienced by individuals with TE as they age [9] reported a high prevalence of musculoskeletal problems, pain or neuropathic symptoms, dental problems, facial damage, and deterioration in sight and/or hearing. As with other physical disabilities, such as cerebral palsy, functional impairment can fluctuate over time [16,17], underlining the importance of regular assessment.

In addition to the ongoing thalidomide-related health difficulties, many individuals also experience a decline in overall health status. In a follow-up to the scoping review, Newbronner et al. [7] quantified the incidence of secondary health problems and their impact on health-related quality of life (HRQOL) and employment. The findings revealed that UK individuals with TE experience the cumulative impact of ageing and a high prevalence of multimorbid illness, including depression and anxiety. These multiple secondary health issues not only affect HRQOL but also impair individual functionality, reducing the ability to work, and driving the need for more assistance in the home [9]. Studies involving individuals with TE in Japan, Sweden, and Germany have also reported a deterioration in general and mental health [6,18,19,20]. Further, comparisons with age-matched populations show more substantial health and physical problems [6,18] and more extensive use of healthcare resources by individuals with TE [6]. Ongoing studies of individuals with TE in these countries [20,21] not only provide insights into the effect of ageing on individuals with TE but show that the

potential for health impairment is cumulative. It requires comprehensive evaluation to inform a healthcare management policy that considers the changing nature of the disabling experience as individuals with TE enter their seventh decade.

Declining physical health and concomitant decrements in reported HRQOL are also observed in other patient communities where the effects of long-term developmental disabilities are exacerbated by increasing age. For example, adults with cerebral palsy report a decline in strength and functional reserve, deterioration in physical activity, and increased risk of musculoskeletal complications with ageing [22]. Ongoing evaluation of health needs can therefore provide greater insight into the time-course of secondary impairments. The Newbronner et al. [7] study examined the secondary health problems experienced by individuals with TE in the UK as they reached their mid-fifties. Although the study showed a cumulative impact of these health problems over time, it did not explore whether there was a difference in their accumulated prevalence compared with people of a similar age in the general population. Therefore, a robust statistical comparison of the impact of secondary health problems on the functionality and overall wellbeing of individuals with TE with that of the general population is needed.

The Thalidomide Trust was established in the UK in 1973 to support individuals with TE and oversee compensation payments made by the drug distributors. In 2016, the Trust began ongoing data collection on health, wellbeing, social circumstances, and current and anticipated care and support needs from the beneficiaries via a Holistic Needs Assessment (HNA). One element of the HNA comprises a quantitative assessment of the presence of health comorbidities unrelated to their embryopathy. These data, collected between October 2016 and December 2019, are the focus of the current report. They are used in a systematic comparison to an age-matched general population using data from the Health Survey for England (HSE) [23] and an analysis of the relationship between the distinctive patterns of TE and specific health conditions. The statistical analysis is based on 392 individuals with TE who represent 94% (392/415) of the total population of those with recognised TE in the UK.

Methods

Participants

At the time of the HNA, 415 individuals with TE were registered with the Trust, resident in the UK, and had the mental capacity to consent and participate in an HNA interview. All were invited to participate by telephone. Of these, 392 gave informed consent to an interview and the use of their anonymised data in secondary analysis. They were between 54 and 60 years at the time of interview (mean age = 56 years; 53% female) (table 1).

Table 1: Profile of the individuals with thalidomide embryopathy participating in the HNA interviews (n=392)

Demographic		% (n)
Gender	Female	53
	Male	47
Accommodation type	House	34
	Other than a house	66
Habitation	Lives alone	23
	Does not live alone	77
Employment	Working	27
	Not working	48
	Status unknown	25

Procedure

The individuals with TE were visited in their homes by one of six interviewers. All of the interviewers had undergone Thalidomide Trust bespoke training, based on the Samaritans' workplace preparation course aimed at equipping people with the skills and confidence to have supportive and effective conversations. Interviewers completed the HNAs using a standardised questionnaire as part of a structured conversation. The quantitative element of the HNA questionnaire (figure 1) contained questions pertaining to 78 self-reported comorbidities grouped across categories such as pain, respiratory, and gastrointestinal illness. Responses were recorded in written form and participating individuals were given the opportunity to review the record of their HNA and correct any errors.

Figure 1: Two sections of the Thalidomide Trust HNA questionnaire that explore the presence of physical health issues, such as problems with pain or digestion, and any issues affecting emotional and mental wellbeing.

Section 2: Health, Lifestyle and Living independently		
Physical health issue	**✓**	**Notes**
Bowel		
IBS ☐ Bowel incontinence ☐ Other bowel problems ☐	☐	
Balance/falls		
Fear of falling ☐ Fallen in last 3 years ☐	☐	
Cancer		
Breast ☐ Bowel ☐ Kidney ☐ Lung ☐ Ovarian ☐ Prostate ☐ Bladder ☐ Other ☐	☐	
Cardio-Vascular		
Blood pressure: High ☐ Low ☐ Normal ☐	☐	
Heart: Heart Attack ☐ Heart Disease ☐ Arrhythmia ☐ Other ☐	☐	
High cholesterol	☐	
Chest		
Asthma ☐ Chest infections ☐ COPD ☐ Other ☐	☐	
Dental		
Dentures ☐ Implants ☐ No teeth ☐ Pain/Decay ☐	☐	
Diabetes		
Type 1 ☐ Type 2 ☐ Normal ☐	☐	
Digestion		
Swallowing issues	☐	
Reflux-gastritis	☐	
Hiatus hernia	☐	
Other	☐	
Ear		
Ear infections ☐ Wax build-up ☐ Other ☐	☐	
Eye		
Eyelid problems ☐ Glaucoma ☐ Infections ☐ Watery☐ Other ☐	☐	
Neurological		
Dementia ☐ Memory loss / problems ☐ Other ☐	☐	
Pain		
Ankle/foot ☐ Calf ☐ Elbow ☐ Hand ☐ Hip ☐ Knee ☐ Leg ☐ Neck ☐ Shoulder ☐ Spine ☐ Thigh ☐ Other ☐	☐	
Pins and needles/numbness		
Arm ☐ Feet ☐ Fingers ☐ Hands ☐ Neck ☐ Toes ☐ Other ☐	☐	
Replacement joint		
Shoulder ☐ Hip ☐ Knee ☐	☐	
Sleep		
Sleep apnoea ☐ Snoring ☐ Other☐	☐	
Thyroid		
Underactive ☐ Overactive ☐	☐	
Urinary		
Incontinence ☐ Other urinary problems ☐	☐	

Section 5: Emotional and Mental Wellbeing		
Emotional and mental wellbeing issue	**✓**	**Notes**
Anxiety	☐	
Loneliness/isolation	☐	
Depression	☐	
Other psychological issues		

Comparison of HNA and HSE Data

The prevalence of comorbidities reported in the HNA was compared with those of an age-matched group (aged 55-64 years) of the general population as reported by the HSE. The HSE survey was initiated in 1991 to monitor trends in the health and care of adults and children living in private households in England [24]. Each annual survey includes health questions and physical measurements such as blood pressure, height, weight, and analysis of blood and saliva samples. There are also questions that differ each year, relating to other health issues or population sub-groups [24]. In 2018, the HSE asked a stratified, multi-stage, random sample of the population of England about long-standing illnesses (defined as 'any physical or mental health condition or illness lasting or expected to last 12 months or more') [23]. Responses were coded into categories defined in the International Classification of Diseases (ICD-10) [25]. To achieve a normative comparison for the HNA data, the first step involved mapping the original 18 HNA categories to the 11 categories included in the 2018 HSE survey (table 2). Three categories in the HSE (skin complaints, blood and related organs, and infectious disease) and two categories in the HNA (sleep issues and balance/falls) could not be matched and were therefore excluded from the comparison.

Table 2: HSE and HNA matched categories of illness[21,23]

HSE illness categories	**HNA categories included in the re-classification**
Nervous system	**Neurological** (dementia, memory loss/problems); **Pain (**locations); **Pins and needles/numbness**
Digestive system	**Digestion** (swallowing issues, reflux-gastritis, hiatus hernia); **Bowel** (irritable bowel syndrome, bowel incontinence); **Dental** (dentures, implants, no teeth, pain/decay)
Mental, behavioural and neurodevelopmental conditions	**Emotional and mental wellbeing** (anxiety, loneliness/isolation, depression)
Ear complaints	**Ear** (infections, wax build-up)
Heart and circulatory system	**Cardiovascular** (blood pressure, heart disease including infarction or arrhythmia)

Respiratory system	**Chest** (asthma, chest infection, chronic obstructive pulmonary disease)
Genito-urinary system	**Urinary** (incontinence)
Diabetes, other endocrine and metabolic	**Diabetes** (type 1, type 2); **Thyroid** (underactive, overactive)
Musculoskeletal system including arthritis/rheumatism/fibrositis; back problems/slipped disc/spine/neck	**Replacement joint** (shoulder, knee or hip)
Eye complaints	**Eye** (eyelid problems, glaucoma, infections, watery)
Cancer (neoplasms) and benign growths	**Cancer** (types/locations)

The second step involved the identification of an age-matched comparison. There are slightly different age distributions across the two comparator samples. Individuals with TE were between 54 and 60 years at interview, with most in the age band 57 to 59 years. HSE reports data by 10-year age bands, split separately between males and females and aggregated overall. Given the age distribution of the individuals with TE (mean age 58 years), the nearest comparative age band from HSE was 55–64. The final consideration was that of geographical distribution. The prevalence of long-standing illnesses in the HSE data was based on adults living in England at the time of the survey. The 392 individuals with TE participating in the HNA resided across the UK: 76% in England, 13% in Scotland, 7% in Wales and 5% in Northern Ireland. It was decided to include all UK data in the analysis.

Classifying thalidomide patterns of impairment

In order to explore the relationship between the patterns of physical impairment caused by TE and the prevalence of health comorbidities recorded in the HNA, four impairment sub-groups were created (A=facial disfigurement or hearing impairment; B=upper limb below elbow (including hand); C=upper limb above elbow; D=lower limb/lower limb+ four limb) (table 3). Of the 392 individuals with TE included in the overall analysis, four were never allocated to a sub-group and died in the period between the HNA interviews and the data analysis. This analysis was therefore based on 388 individuals with TE.

Table 3: Physical impairment sub-groups for individuals with thalidomide embryopathy participating in the HNA interviews (n=388)*

Group title	Description	No of Individuals (n=388)
Group A: Facial disfigurement or hearing impairment	• Damage to face (including eyes/external ears) and/or hearing impairment. No limb damage.	42
Group B: Upper limb below elbow (including hand)	• Damage to hands. No further upper limb damage. No lower limb damage or hearing impairment/facial damage. • Upper limb damage below the elbow. No lower limb damage or hearing impairment/facial damage. • Damage to hands plus hearing impairment/facial damage. No lower limb damage. • Upper limb damage below the elbow plus hearing impairment/facial damage. No lower limb damage.	146
Group C: Upper limb above elbow	• Upper limb damage above the elbow. No lower limb damage or hearing impairment/facial damage Upper limb damage above elbow plus hearing impairment/facial damage. No lower limb damage.	100
Group D: Lower limb/lower limb+ four limb*	• Damage to hands and lower limbs; OR damage below the knee but none to upper limbs. With/without hearing impairment/facial damage. • Upper limb damage above elbow plus damage to lower limbs (above the knee). With or without hearing impairment/facial damage. • Upper limb damage above elbow plus damage to lower limbs (below knee). No hearing impairment/facial damage. • Upper limb damage below the elbow plus damage to lower limbs (above the knee). With or without hearing impairment/facial damage. • Damage to limbs below the elbow and below the knee; OR damage above the knee but none to the upper limb. BOTH with/without hearing impairment.	100
TOTAL		**388**
*Included in the lower limb/lower limb+ group is the small number of people who have lower limb damage only (<5 individuals).		

Statistical analysis

Using SPSS (Version 26), the overall analysis focused on the comorbidities included in the HNA and then matched with the HSE. Prevalence and incidence levels were derived in SPSS as variables for each morbidity before being analysed and reported. Charting and significance testing of comorbidity prevalence levels were conducted in Excel and

compared sub-groups and prevalence levels within the HNA sample with an age-matched sample from the HSE.

Consent and ethics approval

The HNAs are an ongoing element of assessment of the health and wellbeing needs of individuals with TE by the Thalidomide Trust. The aims, design and questionnaire content were reviewed independently by the Health and Wellbeing Committee of the Thalidomide Trust prior to implementation. Additionally, all individuals gave informed consent at two stages: to participate in an HNA, and then for their anonymised data to be used in future secondary analysis. With regard to ethics approval, we referred the project to a university ethics committee. We received the opinion that the research was exempt from further ethical approval as the data involved secondary analysis of aggregated quantitative, fully anonymised data, collected from participants with the capacity to consent.

Results

Health Category Comparisons with the General Population

Independent sample T-tests were used to compare HNA and HSE morbidities. There was a higher reported prevalence of comorbid health conditions amongst the individuals with TE than the HSE comparator group across all 11 overlapping health categories (figure 2). The mean difference in prevalence between our study population and the HSE comparator groups was 24 percentage points and statistically significant across all categories. The greatest differences in the prevalence of self-reported comorbid health conditions between groups were observed in the 'nervous system' and 'digestive system' categories. Ninety-four per cent of individuals with TE reported symptoms of pain, numbness, pins and needles, or neurological problems compared with only 5% in the HSE comparator group. Of these, almost all (366/367) reported symptoms of pain, pins and needles, or numbness, often in multiple locations. The median number of locations reported was five, with over 20% experiencing these sensations in seven or more locations and 10% in nine or more (figure 3). Further, approximately 10% of individuals with TE reported musculoskeletal problems compared with 1.5% of the general population. Gastrointestinal conditions were also highly prevalent amongst individuals with TE compared to the general population (figure 2): 52% reported digestion, bowel, or dental issues compared with 7% in the general population. Forty-

one per cent reported difficulties with mental health compared with 9% of the general population. There were smaller differences in the reported prevalence of genitourinary disorders (10% vs 3%), diabetes and endocrine disorders (19% vs 12%) and cancer (7% vs 3%) (figure 2).

Figure 2: Prevalence of reported morbidities in 11 health categories amongst individuals with thalidomide embryopathy (HNA, n=392) and the general population of England, aged 55-64 (HSE, n=2376)

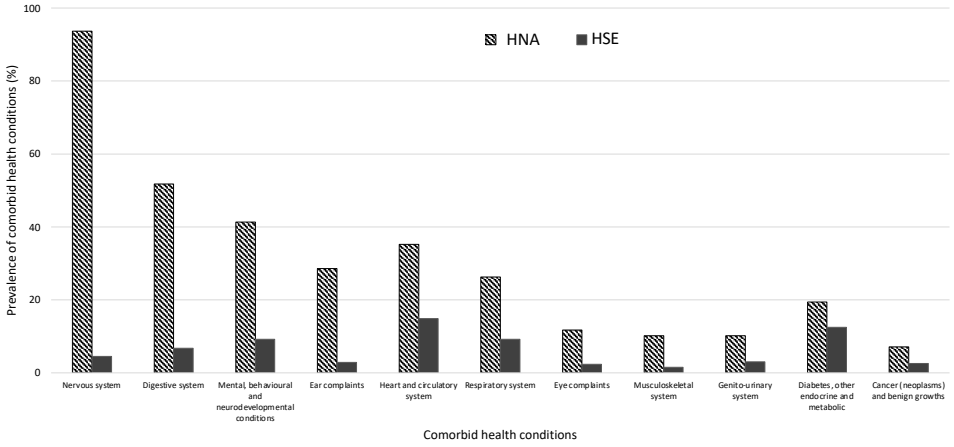


Figure 3: Number of locations affected by pain, pins and needles, and numbness for individuals with thalidomide embryopathy (n=366)

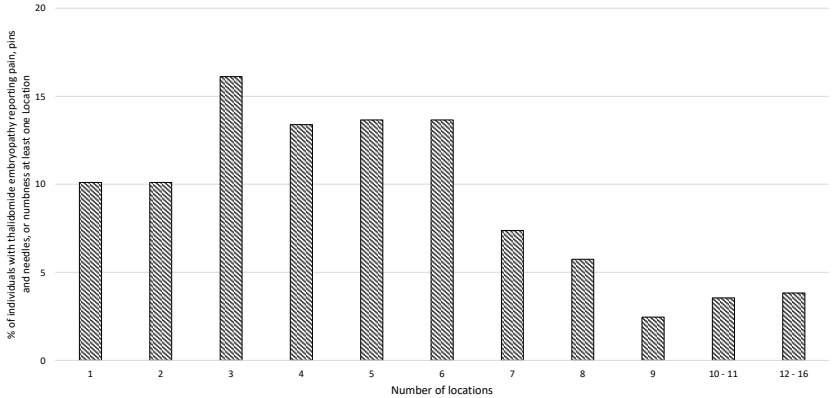
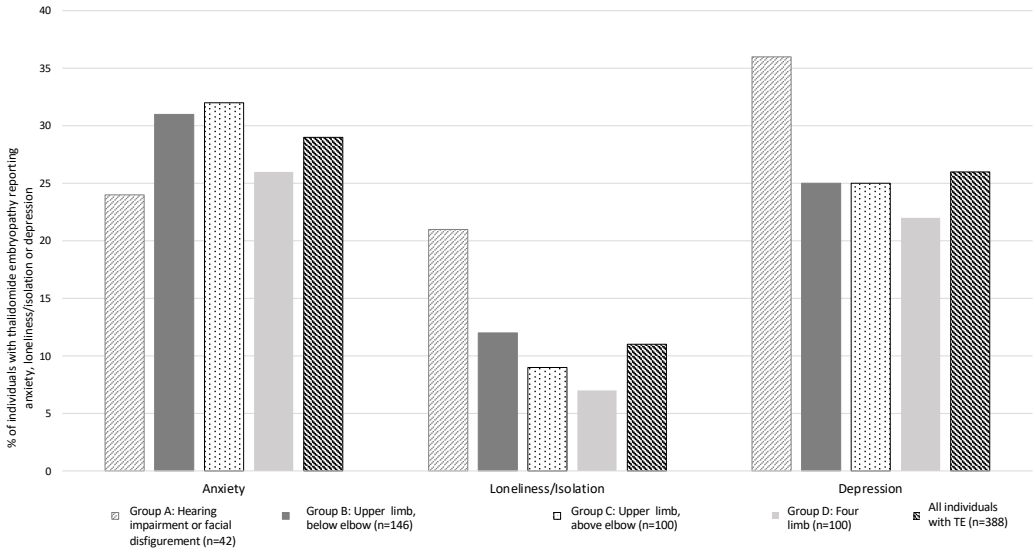


Figure 4: Prevalence of mental health impairment by physical impairment sub-group in individuals with thalidomide embryopathy (n=388)



The relationship between distinctive patterns of TE impairment and self-reported comorbidities

We examined the relationship between the patterns of TE impairment and comorbidities using Z tests. The prevalence of comorbid health conditions (HNA categories) for individuals with TE in the four sub-groups (A–D) was compared with the prevalence of these conditions across the whole cohort. When looking at self-reported physical health conditions, there were three statistically significant differences between the sub-groups and the cohort. Unsurprisingly, there was a greater prevalence of eye or ear problems observed in sub-groups A (facial disfigurement or hearing impairment) (33% vs 12%, $p<0.00001$) and B (impairment to upper limb below elbow (including hand) (39% vs 29%, $p=0.0038$), which also included individuals with TE affected by eye or ear disfigurement. There was also a significant difference in the prevalence of genitourinary complaints between group B and the whole cohort (18% vs 10%, $p=0.001$). The prevalence of self-reported mental health impairment in groups B, C (impairment to upper limb above elbow), and D (impairment to lower limb/lower limb+ four limb) was 40%, 41%, and 39%, respectively, similar to that reported overall (41%). However, for group A, the prevalence of self-reported mental health impairment was greater (52%). When looking specifically at the prevalence of anxiety, loneliness and isolation, and depression across the groups, individuals in group A reported significantly greater

levels of loneliness and isolation when compared with the overall cohort (Figure 3) (21% vs 11%, $p<0.03$) and, although not statistically significant, they also reported a greater prevalence of depression than those in groups B, C and D (36% vs 25%, 25% and 22% respectively).

Discussion

Almost all individuals with TE reported they were affected by comorbid health conditions that have the potential to affect everyday functionality. Although some of these conditions reflect normal age-related deterioration, the comparison of the HNA data with an age-matched sample of the general population from the HSE, highlights that individuals with TE in the UK experience a significantly higher prevalence of these comorbid conditions across all the overlapping health categories in the surveys. Reports of pain and other nervous system impairment are particularly prominent. Almost all individuals with TE report pain, numbness or pins and needles in at least one body area compared with a minority (5%) of the HSE comparator group, findings that reflect those of other studies evaluating the prevalence of chronic pain. Most recently, Niecke et al [20] reported that 94% of individuals with TE reported chronic pain.

Decades of adaptive use, in combination with pre-existing malformations of joints and limbs, is associated with long-term joint damage and pain [12] and overall decline in health status over time [18]. Samel et al. [18] reported a decline in health status in women with thalidomide embryopathy living in Germany over a 13-year period. In 2002, 42% of women (mean age 38, range 35-40 years) reported a statistically significant decrease in their health status compared to the previous year [18]. In 2015, the proportion of women (mean age 51, range 48-53 years) reporting a decline in health status compared to the previous year was 61% [18,26] Although the studies involved only women and a small proportion of the overall individuals with TE population in Germany, they underline the potential for progressive decline in a group already at a substantial disadvantage in terms of health and wellbeing compared to the general population.

More than two-fifths of individuals with TE reported problems with their mental health (anxiety, depression and loneliness) compared to 9% of the general population in the HSE data. Although the HNA data were not collected using validated questionnaires, the self-reported prevalence replicated the findings of a recent survey conducted by Newbronner et al [27] that evaluated the prevalence of depression and

anxiety in individuals with TE using the validated Patient Health Questionnaire (PHQ-9) [27] and the Generalised Anxiety Disorder scale (GAD-7) [28].

Sub-group analysis by pattern of impairment showed a substantial inter-group difference in the reported prevalence of mental health disorders overall and the individual prevalence of anxiety, depression, and loneliness, with those with hearing impairment and facial disfigurement (no limb impairment) the most adversely affected. Notably, this group significantly greater levels of loneliness when compared with the overall cohort. There are few published data regarding the impact of different types of TE on physical or psychological wellbeing. However, Peters et al. [30] also found a higher incidence of depression amongst individuals with TE without limb impairment in Germany. The authors noted that two-thirds of this group were deaf or had a severe hearing impairment and that many also had facial disfigurement [30]. There is also a paucity of data on the experience of loneliness amongst thalidomide survivors and the public in general, despite evidence to show that it can have an adverse effect on health outcomes [31]. These findings make an important contribution to the UK government's strategy, announced in 2018, to gather more data on the experience of loneliness [31].

The majority of individuals with TE with facial disfigurement (group A) are affected by facial palsy, a condition that can impede emotional expression, affect the ability to produce intelligible speech (dysarthria) and chew and swallow normally [32,33]. Problems with speech and communication have been shown to negatively affect HRQOL, particularly in mental and social well-being domains [34] as well as impact Minimum Data Set Health-Status Index (MDS-HSI) scores [35]. Although group A also comprised individuals with TE with hearing impairment, the greater prevalence of depression and loneliness reported reflects the findings of studies involving non-thalidomide populations and its importance should not be under-estimated. Similarly, although our findings describe self-reported symptoms that are not collected using validated questionnaires, they replicate the international evidence showing that the cumulative impact of living with a rare disability [20,21,30,36-39]. The pressures of everyday life, together with the emotional impact of the further loss of function associated with secondary health problems, are linked to a greater likelihood of experiencing mental health disorders [21,30,36-39]. In the recent study by Niecke et al [20], the authors reported a clear correlation between HRQOL impairment the experience of pain and mental health disorders.

This study has multiple strengths, including the fact that it represents 94% of beneficiaries of the Trust living with the consequences of TE in the UK. The findings provide a detailed insight into the prevalence and impact of comorbid health conditions affecting these individuals and can contribute knowledge to those living in other nations. They also replicate and extend the findings of previous UK reports [7,9], where a high prevalence of pain and/or loss of movement in multiple joints, and mental health conditions such as anxiety and depression, were identified. However, the current study goes further; it provides a robust comparison with an age-matched normative sample drawn from HSE data, showing that living with long-term thalidomide embryopathy substantially impacts overall physical health and psychological wellbeing. The results are consistent with international evidence. For example, Hinoshita et al. [6] reported the prevalence of chronic conditions amongst individuals with TE to be more than double that of an age-matched population (69% vs 33%) in Japan. Further, the sub-group analysis of comorbidities linked to patterns of impairment provides critical new insights, revealing that all have the potential increase the prevalence of secondary health conditions, including an increased risk of depression, anxiety, and loneliness. However, individuals with minor impairment to limbs but facial disfigurement are disproportionately affected by mental health disorders.

Limitations of this analysis include the absence of a HRQOL indicator within the HNA survey. Ghassemi Jahami et al. [19] and Niecke et al. [20] found a statistically significant reduction in HRQOL in individuals with TE in Sweden and Germany respectively when compared to the general population. While the impact of pain and other health impairments on HRQOL can be estimated, a validated questionnaire to fully evaluate the impact would provide valuable additional insight. Similarly, more detailed insight into the severity of the health concerns, as detailed in findings by Imai et al. [36] and Samel et al. [18], would be informative. Also, using validated instruments to assess the impact of thalidomide embryopathy on emotional and mental wellbeing would add to existing knowledge across other communities. Specific methodological limitations include the fact that the ICD-10 classification used by the HSE was not an exact match to the categories of the HNA, although mapping across systems was possible. However, the magnitude and statistical significance of differences in the prevalence of all self-reported health issues across the 11 health categories leads to the conclusion that individuals with TE are likely to experience more health issues than a comparable group in the general population. The age distributions across the two

comparator populations also differ slightly. The slightly greater average age of the HSE group would suggest that, if anything, the HNA and the HSE comparator groups slightly underestimate the difference in the number of health concerns between the two populations. However, any reservations about the impact of this age difference are eclipsed by the size of the differences across all morbidities, which supersede any differences due to measurement or sampling error.

Individuals with TE report a higher prevalence of comorbid health conditions across all HSE categories and onset at an earlier age compared to the general population. Although many individuals with TE have maintained independent lives to date, their increasing age and the functional impairment consequent on multimorbidity shown in this analysis raise a concern about the provision of adequate and appropriate healthcare and rehabilitation services in the future. There are multiple opportunities for future research, including extending surveys to other populations who are ageing with severe developmental disabilities, such as cerebral palsy. Assessment of severity, alongside the potential influence of lifestyle and social factors, would also inform the structure and delivery of needs-based care, for example, physical care requirements around joint preservation or joint replacement and rehabilitation. Similarly, the relationship between the reporting of comorbid health conditions and impact on HRQOL and, in turn, its relationship with patterns of impairment would contribute to the individualisation of that care delivery. Finally, the long-term monitoring of multimorbidity compared to the general population, and those with other lifelong debilitative conditions, could contribute to national and global knowledge of the impact of ageing on disability.

Conclusion

This secondary analysis reveals the long-term impact of living with the physical consequences of thalidomide on bodily systems and wellbeing. As they age, these individuals experience the long-term consequences linked to over-use of certain joints, including musculoskeletal and neuropathic pain. Although many have maintained independent lives to date, their increasing age and the associated functional impairment highlight the importance of long-term monitoring of individuals with TE to identify their developing needs and ensure the adequate planning and provision of appropriate rehabilitation services in the future.

Acknowledgements

The authors would like to thank all the beneficiaries of the Thalidomide Trust for their participation in the survey and those beneficiaries who reviewed the research findings within this manuscript. This publication and its content are solely the responsibility of the authors. The HNA research is implemented and funded by the Thalidomide Trust. Medical writing assistance was provided by Lynn Hamilton PhD under the direction of the authors and paid for by the Thalidomide Trust.

Disclosure statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

The research was conducted by the Thalidomide Trust under the guidance of the lead author. All external authors were independent from the researchers and had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity and accuracy of the data analysis.

References

[1] Vargesson N. Thalidomide-induced teratogenesis: history and mechanisms. Birth Defects Res C Embryo Today. 2015;105(2):140–156. https://doi.org/10.1002/bdrc.21096

[2] Vargesson N. Thalidomide-induced limb defects: resolving a 50-year-old puzzle. BioEssays. 2009;31:1327–1336.

[3] McBride WG. Thalidomide and congenital abnormalities. *Lancet* 1961;1:45

[4] Lenz W. Childhood malformations after intake of medication during pregnancy. Dtsch Med Wochenschr. 1961;86:2555.

[5] Vargesson N. Thalidomide Embryopathy: an enigmatic challenge. Dev Biol. 2013;(3):1–18. https://doi.org/10.1155/2013/241016

[6] Hinoshita F, Beppu H, Shioji S, et al. A nationwide survey regarding the life situations of patients with thalidomide embryopathy in Japan, 2018: First report. Birth Defects Res. 2019;111:1633–1642.
[7] Newbronner E, Glendinning C, Atkin K, et al. The health and quality of life of Thalidomide survivors as they age – Evidence from a UK survey. PloS ONE. 2019;14(1):e0210222. https://doi.org/10.1371/journal.pone.0210222
[8] Tajima T, Wada T, Yoshizawa A, et al. Internal anomalies in thalidomide embryopathy: results of imaging screening by CT and MRI panel. Clin Radiol. 2016;71(11):1199.e1–7.
[9] Newbronner E, Atkin K. The changing health of Thalidomide survivors as they age: a scoping review. Disabil Health J. 2018;11:184–191. https://doi.org/10.1016/j.dhjo.2017.09.
[10] Ghassemi Jahani SA, Danielsson B, Karlsson J, et al. Long term follow-up of thalidomide embryopathy: malformations and development of osteoarthritis in the lower extremities and evaluation of upper extremity function. J Child Orthop. 2014;2014(8):423–433.
[11] Ghassemi Jahani SA, Danielsson A, Ab-Fawaz R, et al. Degenerative changes in the cervical spine are more common in middle-aged individuals with thalidomide embryopathy than in healthy controls. PloS One. 2016;11(5): e0155493.
[12] Newman RJ. Shoulder joint replacement for osteoarthrosis in association with thalidomide-induced phocomelia. Clin Rehabil. 1999;13(3)3: 250–252
[13] Miller MT, Strömland K, Ventura L. Congenital aberrant tearing: a re-look. Trans Am Ophthalmol Soc. 2008;106:100–115.
[14] Sjogreen L, Kiliaridis S. Facial palsy in individuals with thalidomide embryopathy: frequency and characteristics. J Laryngol Otol. 2012;126(9):902–906.
[15] Ekfeldt A, Carlsson GE. Dental status and oral function in an adult group of subjects with thalidomide embryopathy – a clinical and questionnaire study. Acta Odontol Scand. 2008;66(5):300–306.
[16] Moll LR, Cott CA. The paradox of normalization through rehabilitation: growing up and growing older with cerebral palsy. Disabil Rehabil. 2013;35(15), 1276-1283. doi:10.3109/09638288.2012.726689
[17] Moll LR, Cott CA. Understanding the Experience of Growing Older with Cerebral Palsy. In Bigby MPC (Ed.), Handbook on Aging with Disability. 2020 (pp83-96). New York and London: Routledge Taylor & Francis Group.

[18] Samel C, Albus C, Nippert I, et al. Life situation of women impaired by Thalidomide embryopathy in North Rhine- Westphalia - a comparative analysis of a recent cross-sectional study with earlier data. BMC Women's Health. 2019;19:51. https://doi.org/10.1186/s12905-019-0745-y.
[19] Ghassemi Jahani SA, Karlsson J, Brisby H, et al. Health-related quality of life and function in middle-aged individuals with thalidomide embryopathy. J Child Orthop. 2016;10(6):691–703. https://doi.org/10.1007/s11832-016-0797-6.
[20] Niecke A, Peters K, Alayli M, Lüngen et al. Health-related quality of life after 50 years in individuals with thalidomide embryopathy: Evidence from a German cross-sectional survey. Birth Defects Res. 2022;114(13):714–724. https://doi.org/10.1002/bdr2.2051.
[21] Imai K, Sone H, Otomo K, et al. Quality of life and pain in patients with thalidomide embryopathy in Japan. Mol Genet Genomic Med. 2020;8e1464.
[22] Yi YG, Jung SH, Bang MS. Emerging Issues in Cerebral Palsy Associated With Aging: A Physiatrist Perspective. Ann Rehabil Med. 2019;43(3):241–49.
[23] National Statistics. Health Survey for England 2018 Longstanding Conditions, 3 December 2019. Available at: https://files.digital.nhs.uk/AA/E265E0/HSE18-Longstanding-Conditions-rep.pdf. (accessed 1 December 2021).
[24] Mindell J, Biddulph JP, Hirani V, et al. Cohort Profile: The Health Survey for England. Int J Epidemiol. 2012;41:1585–1593.
[25] International Classification of Diseases – 10. Available at: https://icd.who.int/browse10/2010/en. (accessed 12 September 2021).
[26] Newbronner E, Wadman R. Depression and Anxiety Symptoms in UK Thalidomide Survivors: A Brief Survey. Disabilities. 2021;1:23–29. https://doi.org/10.3390/disabilities1010002.
[27] Nippert I, Edler B, Schmidt-Herterich C. 40 years later: the health related quality of life of women affected by thalidomide. Community Genet. 2002;5(4):209–216.
[28] Kroenke K, Spitzer R, Williams J. PHQ9: Validity of a brief depression measure. J Gen Intern Med. 2001;16(9):606–613.
[29] Spitzer R, Kroenke K, Williams J, et al. A brief measure for assessing generalised anxiety disorder: the GAD-7. Arch Intern Med. 2006;166:1092–1097.
[30] Peters KM, Albus C, Lungen M, et al. Damage to Health, Psychosocial Disorders and Care Requirements of Thalidomide Victims in North Rhine Westphalia from a Long Term Perspective. Cologne: Federal Health Centre North Rhine Westphalia; 2015.

[31] Office for National Statistics, December 2018. Measuring loneliness: guidance for use of the national indicators on surveys. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/wellbeing/methodologies/measuringlonelinessguidanceforuseofthenationalindicatorsonsurveys. Last accessed: 26 Jan 2022.
[32] Gordin E, Lee TS, Ducic Y, et al. Facial nerve trauma: evaluation and considerations in management. Craniomaxillofac Trauma Reconstr. 2015;8(1):1–13. doi:10.1055/s-0034-1372522.
[33] Tavares-Brito J, van Veen MM, Dusseldorp JR, et al. Facial palsy–specific quality of life in 920 patients: correlation with clinician-graded severity and predicting factors. Laryngoscope. 2019;129(1):100–104. doi:10.1002/lary.27481.
[34] Bruins TE, van Veen MM, Mooibroek-Leeuwerke T, et al. Association of socioeconomic, personality, and mental health factors with health-related quality of life in patients with facial palsy. JAMA Otolaryngol Head Neck Surg. 2020;146(4):331–337. doi:10.1001/jamaoto.2019.4559.
[35] Lam JM, Wodchis WP. The relationship of 60 disease diagnoses and 15 conditions to preference-based health-related quality of life in Ontario hospital-based long-term care residents. Med Care. 2010;48:380–387. doi: 10.1097/MLR.0b013e3181ca2647
[36] Imai K, Toshiharu I, Yamamoto M, et al. Psychological and mental health problems in patients with thalidomide embryopathy in Japan. Psychiatry Clin Neurosci. 2014;68(6):479–486.
[37] Niecke A, Peters K, Samel C, et al. Mental disorders in people affected by thalidomide: a cross-sectional study. Dtsch Arztebl Int 2017;114:168–174.
[38] Kruse A, Ding-Greiner C, Beckerr G, et al. Regular Surveys on Problems, Special Needs and Care Deficiencies of Victims of Thalidomide: Synopsis of Final Report Presented to the Contergan Foundation for People with Disabilities. University of Heidelberg; 2013.
[39] Vermette N, Benegabi M. Study on the current living conditions of Canadian Thalidomide survivors and projections for the future. Thalidomide Victims Association of Canada; 2013. https://thalidomide.ca/wp-content/uploads/2017/12/2013-study-report.pdf (accessed 25 April 2022).