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Published in:
Pain

DOI:
[10.1097/j.pain.0000000000000454](https://doi.org/10.1097/j.pain.0000000000000454)

Publication date:
2016

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

Rice, A. S. C., Smith, B. H., & Blyth, F. M. (2016). Pain and the global burden of disease. *Pain*, 157(4), 791-796.
<https://doi.org/10.1097/j.pain.0000000000000454>

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PAIN

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--Manuscript Draft--

Manuscript Number:	PAIN-D-14-14328R1
Article Type:	Commentary (INVITED ONLY)
Section/Category:	Clinical Epidemiology
Keywords:	Global burden of disease; Pain; epidemiology
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This is the accepted, peer reviewed version of an article published in *PAIN*. The final published version is available online: <http://dx.doi.org/10.1097/j.pain.0000000000000454>

Pain and the Global Burden of Disease

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1. Introduction

From time to time a major global research publication appears which has profound implications for the pain research and clinical management community. The purpose of this article is to draw to the attention of PAIN's readership one such article, The Global Burden of Disease (GBD) Study 2013 which was recently published in the *Lancet* [26]. It comprises a comprehensive and extensive assessment of the global burden of disease down to country level. The GBD Study also documents changes in this burden over a 23 year period ending in 2013. Looking forward, there are plans for these data to be updated on an annual basis.

Here, we summarise, interpret and contextualise the key aspects of the GBD Study 2013 pertaining to pain. What is striking, and indeed highlighted in an accompanying commentary [4], about the morbidity and disability burden data is the high prominence of pain, and diseases associated with pain, as a global cause of disability in both the developed and developing world. Furthermore, an important implication is that whilst some diseases have decreased in prevalence since 1990 (most notably some associated with acute infectious diseases), those burdens associated with chronic pain are in many cases increasing. This is at least partly because of powerful demographic forces such as the aging of populations in the developed world and similarly increased survival into middle and old age in the developing world, resulting both in growing population size and rising prevalence of chronic diseases. In GBD 2010 40% of the overall disease burden in developing countries was due to communicable diseases, 49% to non-communicable diseases (NCDs), and 11% to injuries, and the poorest people in the world were affected at younger ages (40 and under) [27]. In developing countries populations are ageing at a much faster rate than occurred in developed countries: in the UK it took 45 years for the proportion of the population aged over 65 to double from 7% to 14% while it is predicted to take only 14 years in Columbia. To quote Alex Kalache [14] "The developed world became rich before it became old. In developing countries, people are becoming old before they become rich".

2. What did they measure, and how?

The GBD Study 2013 was a major project [26], the paper having 679 co-authors, 58 pages and 1,868 pages of online appendix. Data on 301 diseases and injuries, and 2,337 of their sequelae were drawn from 188 countries, providing systematic evidence on disease burden at global, regional and national levels.

1 For acute conditions (<3 months' duration), the incidence was presented (number of new cases in
2 2013 per 100,000 population); for chronic conditions, prevalence was presented (total number of
3 individuals with the condition in 2013, and the number of individuals per 100,000 population). In
4 addition, the impact of the diseases and their sequelae was calculated as 'Years Lived with Disability'
5 (YLDs) – the prevalence multiplied by a rigorously derived disability weighting factor that represents
6 the public's assessment of the severity of health loss.
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8 The methods are clearly described in the paper and were developed from those used in the 2010
9 GBD study [27], and results were compared with the re-analysed results of the first GBD study,
10 which was in 1990.
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12 13 14 15 *3. The global burden of disease – a painful picture*

16 The GBD Study showed that only a small fraction of the world's population (4.3%) was free of
17 disease, injury or sequelae. Because of increases in world population and life expectancy, the total
18 number of individuals suffering almost every condition increased, and the prevalence of multi-
19 morbidity also increased. Furthermore, mortality was found to be declining faster than disease
20 prevalence and disability, with a resultant growth in the overall burden of disease. In other words,
21 while life expectancy has increased, healthy life expectancy has not kept pace.
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24 The commonest acute conditions, by far, were upper respiratory infections with in excess of 18.7
25 billion cases in 2013, increased by 38% in number since 1990, and 6.5% in age-standardised rate.
26 Most of the commonest acute conditions were infectious diseases and short-term injuries, but tooth
27 pain due to permanent caries was the 5th commonest acute condition, with more than 200 million
28 cases estimated in 2013 (an absolute increase of 36% since 1990, and a rate increase of 1.4%).
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31 A total of 59 chronic conditions were estimated each to have a global prevalence in excess of 1%,
32 with eight conditions affecting more than 10% of the global population. The commonest of these
33 was asymptomatic dental caries (2.4 billion individuals, rising from 1.7 billion in 1990). Second
34 commonest (and therefore the commonest symptomatic chronic condition) was recurrent tension-
35 type headaches (1.6 billion in 2013, up from 1.1 billion in 1990); the age-standardised rate of this
36 condition was unchanged in the comparison period. Seven of the commonest chronic conditions
37 were found to be primary pain conditions – migraines were the 7th commonest, low back pain was
38 12th, neck pain was 19th, 'other musculoskeletal conditions' were 32nd, osteoarthritis 33rd, and
39 urolithiasis was 57th. Although these all demonstrated large increases in total numbers of individuals
40 affected, the age-standardised rates of chronic conditions were mostly either unchanged or only
41 slightly reduced in comparison with 1990. Only five conditions demonstrated an increase in rate,
42 including 'other musculoskeletal conditions', for which a 6.6% increase in rate was estimated, and
43 urolithiasis (20.1% increase).
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49 Probably, though, the most important picture of disease burden is represented by the YLDs, which
50 take both the prevalence and severity into account. YLDs describe the impact of conditions on
51 individuals, and by implication on their communities and societies, and the health and social services
52 which must provide for them. Many of the most prevalent conditions (e.g. asymptomatic dental
53 caries) are found to contribute less to YLDs, because of relatively low disability weightings. It is
54 therefore in examining causes and rates of YLDs around the world that we find chronic pain to be
55 the most important condition – globally, regionally, and in every individual country. It should be
56 noted that for some regions (especially developing country areas such as Sub-Saharan Africa) there
57 were no or scant primary data and the YLDs were estimated from the population structure and
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1 weighted prevalence rates from other regions. There is still a great need for primary data from these
2 areas to improve burden estimation.

3 Globally, the single greatest cause of YLDs was chronic low back pain, which was estimated to cause
4 more than 146 million YLDs in 2013, an increase of 61% since 1990 (with no significant change in
5 age-standardised rate). This compares with the second greatest cause – major depressive disorder –
6 which contributed in excess of 51 million YLDs (increased in number by 53% since 1990, and in rate
7 by 4.7%). Chronic neck pain was the 4th greatest cause (>34 million YLDs); migraine was 6th (>28
8 million YLDs); ‘other musculoskeletal disorders’ was 10th (>22 million YLDs); osteoarthritis was 13th
9 (>12 million YLDs); and medication overuse headache was 18th (>9 million YLDs). The main four
10 chronic pain conditions featured in the top ten causes of YLDs both in developed countries and in
11 developing countries.
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15 Indeed, chronic back pain and chronic neck pain featured in the top ten causes of YLDs in every
16 country examined, and migraine was also ranked in the top ten everywhere other than Sub-Saharan
17 Africa. Musculoskeletal disorders together with fractures and soft tissue injuries accounted for
18 20.8% of all YLDs globally in 2013. Mental health conditions were also important causes of YLD, with
19 major depressive disorder appearing in every country’s list of top ten causes, and anxiety featuring
20 prominently; both of these are important co-morbidities with chronic pain. Regions with notable
21 variation from the most important global causes of YLDs were Africa and the Middle East. In North
22 Africa and the Middle East, opioid use disorder was listed as the 8th most important cause (and the
23 most important in Qatar). Data for every country and condition assessed are available as
24 supplementary tables in the paper’s extensive online appendix.
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29 The study was designed to assess the global burden of disease, and cannot provide definitive
30 explanations for the findings. However, the authors postulate that the main reasons for the increase
31 in YLDs caused by these chronic pain conditions are related to ageing populations (rates of YLDs are
32 declining much more slowly than mortality rates), increasing obesity and reducing levels of physical
33 activity. Rates of obesity, road traffic accidents, other types of injury are all increasing in the
34 developing world. They further note that there is still little policy discussion around their prevention
35 and management, despite their burden being highlighted as larger than expected in the GBD 2010
36 Study [27].
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42 *4. The burden of “hidden” pain*

43 The preceding section documents how chronic pain is clearly the most important current and future
44 cause of morbidity and disability across the world, with large recent increases in both the number of
45 individuals affected and years lost to disability, coupled with static or rising prevalence rates.
46 However, even this picture actually under-estimates the total burden imposed by chronic pain. Here
47 we discuss a number of disparate exemplar conditions where pain can be a major feature, although
48 it was not possible to ascertain the exact contribution of pain to the overall YLD from the published
49 GBD data.
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53 The diabetes pandemic is well documented and diabetes was ranked as the 7th most important
54 cause of YLDs globally, rising from 10th in the 1990 survey – a percentage change of 136% and now
55 accounting for 29 .5 million YLD. Up to 26% of type 2 diabetics suffer from painful diabetic
56 neuropathy, representing a population prevalence of 0.8% [25].
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1 With respect to infectious diseases, in Sub-Saharan Africa, diseases arising from HIV/AIDS (other
2 than mycobacterial infection) were listed as the 4th most important cause of YLDs, and were top of
3 the list in six countries. The number of YLDs caused by HIV-related diseases, standing at >4 million in
4 2013, had increased by more than 300%, with an age-standardised rate increase of 172% since 1990.
5 HIV/AIDS is associated with many causes of pain, but one of the most relevant, especially as the
6 trend towards to world-wide access to antiretroviral drugs continues, is HIV-associated sensory
7 neuropathy (HIV-SN). The anticipated decline in HIV-SN with withdrawal of neurotoxic antiretroviral
8 drugs is not yet evident and this peripheral neuropathy still afflicts between 27% and 57% of people
9 living with HIV of whom between 38% and 90% experience neuropathic pain [8; 11; 21]. Therefore,
10 HIV-SN is one of the most frequent manifestations of HIV in people who are adequately treated with
11 antiretroviral drugs. The burden of neuropathic pain in HIV-SN is further increased as it is peculiarly
12 resistant to analgesic therapies which are effective in other painful neuropathies [9; 12; 22; 23].
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16 Varicella and herpes zoster were globally associated with 198,000 YLDs, having increased by 48%
17 since 1990, although there was a slight decline when the age-standardised change was taken into
18 account. However, it is not possible to ascertain to what extent this is attributable to the main
19 chronic pain complication of zoster, postherpetic neuralgia. Whilst postherpetic neuralgia would be
20 expected to become more prevalent with an ageing population, this may well be mitigated by the
21 ongoing introduction of zoster vaccination in a number of countries [20].
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24 Although now a comparably rare disease globally, leprosy is still prevalent in parts of the developing
25 world and accounted for some 40,000 YLDs, these having increased by 73% since 1990 (age
26 standardised increase 6%). Some of this burden is probably attributable to neuropathic pain, which
27 chronically afflicts some 20-25% of leprosy patients even long after mycobacteriological cure,
28 because of persisting nerve damage and new immune mediated neuritis reactions [13; 18; 24].
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31 Overall cancer accounted for 6.8 million YLDs, an increase of 83% (age adjusted 8.5 million YLDs).
32 Neuropathic or mixed pain has been found to affect 20-40% of people with cancer [5]. These findings
33 are importantly contextualised by considering ongoing gains in cancer survival for many common
34 cancers.
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37 We are increasingly aware of the importance of neuropathic pain in neurological disorders and it is
38 notable, for example, that multiple sclerosis and Parkinson's disease accounted for 755,000 and
39 695,000 YLDs respectively, both having increased since 1990.
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42 Sickle cell disorders and trait accounted for 342,000 and 1.4 million YLDs respectively.
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44 Disability following war and conflict were ranked as the top causes of YLDs in Cambodia, Nicaragua,
45 and Rwanda and second in Vietnam. Modern munitions dictated that limb trauma and amputation
46 (and therefore post amputation pain) were one of the major survivable injuries of the First World
47 War [10] and this continues to be a major feature of modern day conflicts, including those inflicted
48 on civilians by landmines long after active conflicts have finished [3; 7; 16; 17; 19].
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51 Finally, the contribution of harms associated with analgesic treatments to the global burden of
52 disease cannot be ignored, although it is difficult to ascertain the exact impact of prescribed, as
53 opposed to misused, therapies. Overall the adverse effects of medical treatment globally accounted
54 for 201,000 YLDs. Nevertheless, it is sobering to note in passing that opioid use disorders accounted
55 for 5.8 million YLDs and medication overuse headache for 9.8 million, with both having risen since
56 1990. Cannabis is often advocated for the treatment of pain, particularly neuropathic pain, despite a
57 distinct lack of evidence for efficacy and unknown risks of harm [12] – cannabis use disorders
58 accounted for 396,000 YLDs.
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5. Implications for pain research, practice and policy.

GBD 2010 [27] and 2013 [26] changed our understanding of the huge global burden of disease that is driven by pain conditions, and also highlighted areas where the pain community can contribute to further improvements in how this burden is accurately assessed and, ultimately, reduced. This global challenge requires an agenda and action plan that must span research, policy and practice, and actively address the problems pertaining both to developed and to developing countries.

The over-arching priority is global recognition of chronic pain as a distinct clinical entity, rather than merely as a symptom of other conditions, with funding specifically identified and allocated to address this most disabling of conditions across a diverse range of diseases and settings.

5.1 Research

Pain research has historically been – and continues to be - a low priority for research funders; for example in 2007 only 0.61% of the United States National Institutes of Health budget was allocated to pain research [1]. Funding for clinical services has been similarly problematic.

Experience to date with estimating the global burden of pain has identified significant gaps in our basic understanding of how pain affects populations, ranging from the prevalence of common pain conditions to the cultural dimensions of pain burden (such as stigma and shame) in different societies.

We need population studies that measure burden of pain (occurrence and impact) in countries where no primary studies have been done, most notably in developing countries and regions such as Sub-Saharan Africa. This will first require the development of standardised and robust measures for use in population studies of common pain-associated conditions such as neck pain. Then we need better characterisation of the natural history and main trajectories of common pain conditions so that incidence and remission rates, as well as prevalence rates and the proportions who experience pain-related disability at all levels of severity, can be better understood. There is a need for better measurement of neuropathic and disease-associated pain, and a more consistent approach to characterising pain as a sequel of injury (for example, spinal cord injury), surgery or disease.

New population-level studies are also needed to assess how the cross-cutting risk factors for chronic diseases – such as poverty, diet, obesity, physical activity levels and other common exposures associated with chronic diseases – interplay with pain within an explicit public health framework [6]. Linked to this will be the identification and implementation of policy and political approaches to reducing the burden of chronic pain. These are at least as important as clinical interventions, given the association of chronic pain with poverty and secular demographic trends in the societies affected.

5.2 Practice

A number of areas of clinical practice require scrutiny in the light of the high visibility of pain in the GBD picture. However, those of us involved in clinical pain management should also recognise that our efforts are likely to be more effective if they are conducted not in isolation, but rather imbedded as part of an overall multi-disciplinary rehabilitation programme aimed at returning individuals to functioning as productive members of their societies.

To directly address the burden of disease, research must continue to identify and evaluate new clinical interventions for chronic pain, including its prevention. These will include a range of modalities and/or be multi-modal, including pharmacological, physical, psychological, social and

1 surgical. Nevertheless, for effective translation of new and existing evidence on prevention and
2 treatment into clinical practice it is arguably time for the international pain community to become
3 more active in adopting emerging key factors in successful translation and implementation from the
4 rapidly developing field of implementation science.

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6 However, changing practice is not just about introduction of novel interventions, but also,
7 importantly, implementation of existing evidence-based effective, and cost-effective, treatments for
8 chronic pain throughout community, primary care and specialist care settings (see for example:
9 Scottish Intercollegiate Guideline Network guidelines (SIGN) [2]. These include many interventions
10 that are relatively inexpensive (e.g. self-management; physical activity) and that are suitable for
11 delivery to large numbers of people in low resource settings. Associated with this is the development
12 of “minimum” and “optimum” standards of pain service provision appropriate to each country,
13 including staffing levels and increased local availability of appropriate drugs on the WHO Essential
14 Medicines Lists [15]. International review and comparisons of current service provision in
15 comparison with such standards will be essential, as will strategies to bridge the gaps.

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17 Finally, as ever, appropriate education of healthcare professionals and managers, patients, and
18 society in the mechanisms, prevention and management of chronic pain is vital.

19 20 21 22 *5.3. Implications for policy*

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24 We need to articulate a coherent and integrated framework for pain conditions, to be used within
25 the GBD and other policy contexts. This should to replace the somewhat fragmented and
26 conceptually clouded approach to date in which some, but not all, common regional pain conditions
27 are included, where pain is not explicitly included as an important sequel of other conditions, and
28 the role of pain as a risk factor for other conditions is not well-conceptualised. Despite the current
29 approach, enough is known about the global pain burden to warrant significant responses from
30 global and national agencies. The WHO’s focus on non-communicable diseases remains on
31 cardiovascular and respiratory diseases, diabetes and cancer. This is noteworthy, as there is little to
32 suggest to date that there has been significant institutional response to the GBD evidence about
33 pain burden. It is incumbent on the pain community to engage with the ongoing GBD initiative, and
34 to advocate globally, for action and progress on the universal burden of pain.

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39 The difficulties of undertaking research and interventions in resource-poor countries are substantial
40 and are likely to require active engagement with the WHO, the United Nations, and potentially
41 partnering with other professional associations. For example the Bone and Joint Decade
42 (www.bjd.org.au) notably played a key role in supporting the work of the expert reference group for
43 musculoskeletal conditions in GBD 2010. Much of this research is likely to be done by researchers
44 whose primary expertise is not in pain research (for example, studies where pain is the sequel of
45 other conditions), again pointing to the importance of collaborations and partnerships. Another
46 form of engagement would be for members of the international pain community with the relevant
47 expertise to have direct input through the GBD collaborators network (www.healthdata.org/gbd).

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51 In conclusion, GBD 2013 [26] has changed our understanding of the huge burden of disease and
52 disability that is driven by pain-associated conditions and places chronic pain firmly at the crux of
53 healthcare provision - this has major societal implications for research, planning, delivery and
54 resource allocation. Looking forward and empowered by this knowledge, it is incumbent on the
55 global pain research and clinical communities to recognise and address this challenge, interact with
56 and influence the GBD programme and its methods, and advocate for a better and more detailed
57 understanding of pain as the major component of global disease burden. *Carpe diem!*

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Conflict of interest statement: ASCR and BHS have no conflict to declare. FMB is an author of the GBD study