PharmacoEconomics (2016) 34:1277–1297
DOI 10.1007/s40273-016-0441-9

ORIGINAL RESEARCH ARTICLE

Nocturia Work Productivity and Activity Impairment Compared with Other Common Chronic Diseases

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Published online: 31 August 2016

Abstract

Objectives The International Continence Society defines nocturia as the need to void one or more times during the night, with each of the voids preceded and followed by sleep. The chronic sleep disturbance and sleep deprivation experienced by patients with nocturia affects quality of life, compromising both mental and physical well-being. This paper aims to characterise the burden of nocturia by comparing published data from patients with nocturia with data from patients with any of 12 other common chronic conditions, specifically focusing on its impact on work productivity and activity impairment, as measured by the instrument of the same name (WPAI).

Methods A systematic literature review of multiple data sources identified evaluable studies for inclusion in the analysis. Study eligibility criteria included use of the WPAI instrument in patients with one of a predefined list of chronic conditions. We assessed the quality of each included study using the Newcastle–Ottawa scale and extracted basic study information, work and activity impairment data. To assess how work and activity impairment from nocturia compares with impairment from other common chronic diseases, we conducted two data syntheses (pooled and unpooled).

Results The number of evaluable studies and the range of overall work productivity impairment reported, respectively, were as follows: nocturia (3; 14–39 %), overactive bladder (5; 11–41 %), irritable bowel syndrome/constipation (14; 21–51 %), gastroesophageal reflux disease (GERD) (13; 6–42 %), asthma/allergies (11; 6–40 %), chronic obstructive pulmonary disease (COPD) (7; 19–42 %), sleep problems (3; 12–37 %), arthritis (13; 21–69 %), pain (9; 29–64 %), depression (4; 15–43 %) and gout (2; 20–37 %).

Conclusions The overall work productivity impairment as a result of nocturia is substantial and was found to be similar to impairment observed as a result of several other more frequently researched common chronic diseases. Greater awareness of the burden of nocturia, a highly bothersome and prevalent condition, will help policy makers and healthcare decision makers provide appropriate management of nocturia.

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Key Points for Decision Makers

This paper characterises the available evidence on the burden of nocturia and provides context by comparing data from patients with nocturia with data from patients with any of 12 other common chronic conditions, specifically focusing on the effects of nocturia on work productivity and activity impairment.

Overall work productivity impairment as a result of nocturia is substantial and similar to impairment observed as a result of several other more frequently researched common chronic diseases that physicians may more actively manage.

Greater awareness of the burden of nocturia, a highly bothersome and prevalent condition, will help policy makers and healthcare decision makers provide appropriate management of nocturia.

1 Introduction

The International Continence Society defines nocturia as the need to routinely void one or more times during the night, with each of the voids preceded and followed by sleep [1], with two or more voids per night established as an average threshold of bothersomeness [2]. The chronic sleep disturbance and sleep deprivation experienced by patients with nocturia affects their entire health-related quality of life (HRQoL), compromising both mental and physical well-being. While it is well established that the prevalence of nocturia increases with age [3], prevalence among those aged 40–65 years is reported to be as high as 50 % [4]. The burden of many chronic diseases on HRQoL is well documented, including—often where multiple age groups are affected—the impact on work productivity and activity impairment. This impact of nocturia and, indeed, how it may compare with the impact of other chronic diseases is less well documented.

1.1 Description of the Condition

Lower urinary tract symptoms are often taboo, and patients are therefore hesitant to seek help [5]. Nocturia was not defined as a standalone symptom before 1999 [6], but it is still often only understood as a symptom of overactive bladder (OAB) and benign prostatic hyperplasia (BPH). Discussion is ongoing as to whether a diagnosis of BPH and especially OAB is too broad and symptom based and leads to misdiagnosis and inappropriate treatment [7].

The medical definition of nocturia is abnormally excessive urination during the night. Nocturia may be a symptom of systemic disease. Nocturia without polyuria (the passage of large volumes of urine with an increase in urinary frequency) can be a consequence of (1) loss of normal diurnal variation in solute excretion because of oedema-forming states: congestive heart failure, cirrhosis and nephrotic syndrome; chronic renal disease; advanced age and side effects from drugs (β-adrenergic blockage, diuretics); and (2) loss of renal-concentrating ability because of chronic renal disease or malnutrition. Nocturia with polyuria (about 75 % of the nocturia cases [8]) can be a consequence of (1) water diuresis associated with pituitary or nephrogenic diabetes insipidus or psychogenic water drinking, (2) solute diuresis because of endogenous or exogenous factors and (3) combined water and solute diuresis. Pathophysiologically, nocturia is largely attributed to nocturnal polyuria (nocturnal urine overproduction generally defined as >33 % or 24-h urine volume), which is often due to an altered endogenous production of arginine vasopressor hormone.

This paper highlights what is known about the burden that nocturia places on patients in terms of its impact on work productivity and activity impairment relative to other generally more well-researched common chronic diseases. This greater awareness of the burden of nocturia, a highly bothersome and prevalent condition, will help policy makers and healthcare decision makers to provide appropriate management of nocturia.

1.2 Objectives

Our objective was to characterise the burden of nocturia by comparing data from patients with nocturia with data from patients with any of 12 other common chronic conditions, specifically focusing on the effect on work productivity and activity impairment, as measured by the instrument of the same name (WPAI) [9].

2 Methods

2.1 Types of Studies

In the literature searches, we placed no restriction on study design, including both observational and interventional studies and recording study design. For interventional studies, we used only baseline WPAI data in this review. Extracted data from studies with concurrent control groups, matched case–control studies, are presented by study arm. We also included data from cohort studies in the review.

We conducted systematic electronic searches of MEDLINE (PubMed), Embase, EconLit, Cochrane Database of Systematic Reviews (DSR), the American College of Physicians (ACP) Journal Club, and the Database of Abstracts of Reviews of Effects (DARE), with no restrictions on publication date or language. We used a pragmatic selection of a wide range of chronic diseases affecting physical and mental health as well as multiple aspects of HRQoL, did not apply any filters to restrict searches to specific study designs and used the following specific search terms: WPAI nocturia, WPAI OAB, WPAI IBS, WPAI constipation, WPAI GERD, WPAI asthma, WPAI rhinitis/allergy, WPAI COPD, WPAI sleep, WPAI arthritis, WPAI pain, WPAI depression and WPAI gout. We also conducted a systematic search of the WPAI registry of studies [15], a voluntary registry to which authors can submit publications of studies involving the WPAI instrument.

2.2 Types of Outcome Measures

Work productivity is increasingly recognised as a valuable way to capture the multifaceted impact of chronic health issues on patients' lives. The frequently used validated measures include the WPAI [9], the Health and Labour Questionnaire (HLQ) [10], the Work Limitations Questionnaire (WLQ) [11], the Work Ability Index (WAI) [12] and the Health and Work Productivity Questionnaire (HPQ) [13]. To date, the impact and burden of nocturia has been under researched; the modified WLQ [11] has been used in studies of OAB with nocturia [14], but only the WPAI [9] instrument has been used in studies specific to patients with nocturia. The WPAI measure has been extensively used to study many other health issues. Since comparison across different measures is problematic, we selected work productivity and activity impairment specifically measured by the WPAI [9] instrument as the primary outcome measure for this study.

The WPAI instrument produces four outcome measures: (1) the percentage work time missed due to the specific health problem; (2) the percentage impairment while working due to the specific health problem; (3) the percentage overall work impairment (1 + 2) due to the specific health problem; and (4) the percentage activity impairment[1] due to the specific health problem. Studies reporting at least one of these outcome measures were eligible for inclusion in this review.

The WPAI instrument is free to use and not licensed. The authors' instructions for use state that the questionnaire cannot be called the WPAI if questions or responses are changed or questions are added or deleted. Three primary versions of the WPAI instrument exist, with only slight variations in the wording used. In the general health version (WPAI: GH), respondents are asked questions about work and activity impairment due to health problems. In the specific health problem version (WPAI: SHP), respondents are asked questions concerning impairment due to the target health problem (e.g. arthritis). In the combination version, WPAI: GH/SHP respondents are asked about impairment due to a specified health problem and impairment due to other health reasons. The WPAI can be adapted to a specific disease or health problem; if no other changes are made, the resulting instrument can be referred to as the WPAI. Users are cautioned that although the discriminative validity and reproducibility of the SHP version has been established, evidence for evaluative validity and responsiveness to clinically meaningful change has only been established for some diseases [15]. For peer-reviewed studies included in this review, we assumed the WPAI instrument was used in accordance with its authors' instructions.

2.3 Types of Participants

For this study, we were primarily interested in participants with nocturia. Once we had selected the WPAI instrument as the primary outcome measure, we reviewed the full WPAI database of studies [15][2] and made a pragmatic selection of a list of chronic diseases for which multiple WPAI studies had been completed, applying no other criteria to the selection of comparison studies. Of course, further comparison with other WPAI studies is feasible.

Patients with any of the following 12 common chronic conditions[3] were included in the review: OAB, COPD, IBS, constipation, sleep problems (with multiple factors),

[1] WPAI instructions for activity impairment: "By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal."

[2] The WPAI database of studies (http://www.reillyassociates.net/WPAI_References.html) includes the following health issues: anemia, angioedema, ankylosing spondylitis, arthritis, asthma/allergies, cancer, caregivers, Crohn's disease, chronic obstructive pulmonary disease (COPD), dermatology, diabetes, dyspepsia, erectile dysfunction, eye disease, gastroesophageal reflux disease (GERD), general health, gout, headache, hepatitis, HIV/AIDS, hypertension, inflammatory bowel disease, irritable bowel syndrome (IBS)/chronic constipation, lupus, mental health, multiple sclerosis, neurology, nocturia, obesity/nutrition, OAB, pain, peripheral artery disease (PAD), respiratory, restless legs syndrome, rhinosinusitis, sleep, spondyloarthritis, substance abuse, ulcerative colitis, urinary incontinence, voice disorders, women's health.

[3] For analysis, constipation is combined with IBS, and asthma is combined with rhinitis/allergies, hence 12 common chronic conditions are organised into ten categories to compare with nocturia.

asthma, arthritis, depression, pain (from multiple causes), rhinitis/allergies, GERD or gout.

Participants in studies reporting work productivity and activity impairment are predominantly but not exclusively in paid employment. We placed no restriction on the nature of a participant's employment for this review. The WPAI instrument instructions for use require that only data on activity impairment are collected for participants who are not employed.

2.4 Data Collection and Analysis

2.4.1 Selection of Studies

Two researchers (PM, HH) independently applied the inclusion/exclusion criteria to the selection of studies and, after reconciliation, reached agreement. Figure 1 is a preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram [16] showing the study selection process. After we removed duplicate publications, we screened records and excluded any that were found to be multiple publications of the same WPAI study data, contained insufficient WPAI data for the objective of this review, or studied disease areas outside the scope of this review (acute or less common conditions).

2.4.2 Data Extraction and Management

The researchers completed a data abstraction form summarising the study design, study population, method of exposure assessment, and analysis methods for each included study. This form was informed by the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement [17]. Data on participants' primary health condition, subgroup (if any), age, sex and country of residence were extracted for tabulation. For case–control studies, all data were also extracted and presented for control groups as well as statistical analyses comparing groups.

We assessed the quality of all included studies using the Newcastle–Ottawa scale [18], which is included in the Cochrane handbook [19] of methods for reviewing non-randomised studies. The Newcastle–Ottawa scale assesses

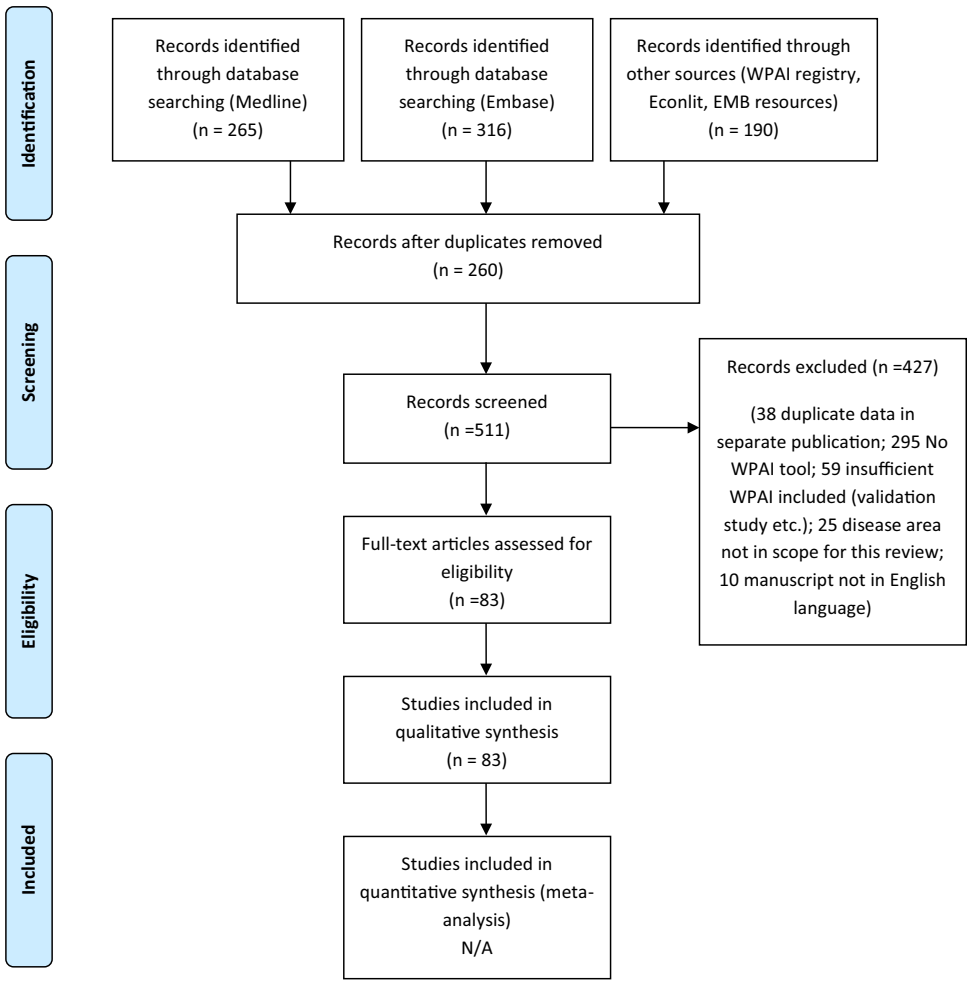


Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of study selection process. *WPAI* Work Productivity and Activity Impairment, *N/A* not applicable

a study on three broad perspectives: selection of study groups, comparability of study groups, and ascertainment of either the exposure or the outcome of interest for case–control or cohort studies, respectively. A study can be awarded a maximum of one star for each of four numbered items within the selection category and three numbered items in the exposure/outcome categories. A study can obtain a maximum of two stars for the comparability category.

2.4.3 Data Synthesis

It was difficult to conduct a meta-analysis of WPAI data from these studies because data at the study level was insufficient for us to make any informed judgements to control for relevant patient-, disease- or job-related covariates; patient-level data were unavailable. We conducted two data syntheses to assess how work and activity impairment as a result of nocturia compares with impairment as a result of other common chronic diseases. First, we collated (but did not pool) all evaluable WPAI data by disease area to show the range of estimated work and activity impairment within and across disease areas. Second, we pooled and weighted all evaluable work and activity impairment data by study size to provide a central estimate for each disease area. We plotted disease area work and activity impairment estimates within the observed range for each disease area to show how they compared within and across disease areas.

In addition, to highlight how the different nocturia subgroups compared with other disease areas, we organised the full dataset of all evaluable work and activity impairment data, including all reported subgroups, in descending order of impairment. Comparative rank order for nocturia studies is reported for both overall work impairment and overall activity impairment.

3 Results

3.1 Included Studies

We included 84 studies in the review: three nocturia studies [20–22], five OAB studies [23–27], 14 IBS/constipation studies [28–41], 13 GERD studies [42–54], 11 asthma/allergies studies [55–65], seven COPD studies [66–72], three sleep studies [73–75], 13 arthritis studies [76–88], nine pain studies [89–97], four depression studies [98–101] and two gout studies [102, 103].

Table 1 shows the baseline characteristics of studies collated by disease area. As expected, the number of studies and evaluable patients was lower for nocturia than for other disease areas. The overall evaluable sample for nocturia was very similar in age to the sample for OAB, COPD and gout, whereas studies of other disease areas involved younger patients. Studies of nocturia, COPD and gout predominantly involved male patients, whereas others involved predominantly females. The evaluable samples for nocturia and OAB included international studies, whereas other disease areas were more likely to be from single countries.

The included studies are presented in Table 2 (cohort studies) and Table 3 (case–control studies). The total evaluable dataset for this review, including all subgroups and controls reporting at least one WPAI outcome measure, consisted of 113 groups (all rows of Tables 2 and 3).

Table 1 Analysis of baseline characteristics

Study condition	Evaluable studies (*n*)	Maximum evaluable sample with condition	Weighted mean[a] age	Weighted mean[a] % male	Weighted mean[a] study setting (single country = 0, international study = 1)
Nocturia	3	3092	60	59	0.9
OAB	5	5510	61	29	0.6
IBS/constipation	14	15,367	43	19	0.3
GERD	13	14,795	49	45	0.01
Asthma and allergies	11	14,212	43	38	0.19
COPD	7	7974	59	59	0.33
Sleep	3	5622	51	39	0
Arthritis	13	11,257	55	40	0.26
Pain	9	7572	46	31	0.07
Depression	4	20,796	48	26	0
Gout	2	21,983	61	81	0.01

COPD chronic obstructive pulmonary disease, *GERD* gastroesophageal reflux disease, *IBS* irritable bowel syndrome, *OAB* overactive bladder

[a] Weighted by study size

Although most studies used the WPAI: SHP version of the instrument, 16 used WPAI: GH[4] (essentially those that assessed multiple diseases within the same study).

Tables 2 and 3 show the quality assessment of each included study according to the three Newcastle–Ottawa scale categories [18]. Overall, cohort studies scored relatively poorly, scoring either one or two stars (out of a possible four) on the selection criteria due to representativeness of the exposed cohort or ascertainment of the exposure; few studies scored stars on the comparability criteria, where study design or analysis must show how confounding factors are controlled; and no studies scored stars on the outcome criteria—essentially because WPAI is a self-report measure, data were cross-sectional and studies did not report the handling of non-response/missing data in sufficient detail. As expected, case–control studies generally scored more highly on the quality-assessment scale, included studies scored well on the selection criteria (three or four stars out of four); all studies scored a maximum of two stars on the comparability criteria; most studies scored one star (out of three) on the exposure criteria.

3.2 Excluded Studies

We excluded 427 of the publications that were initially identified during the searches: 295 did not present WPAI data; 59 had insufficient WPAI data—most of these were validation studies testing psychometric properties of the instruments in various diseases; 68 were identified as multiple publications of another WPAI dataset; 25 presented data on diseases outside the scope of this review (e.g. breast cancer); ten were published in languages other than English.

3.3 Effects on Work Productivity and Activity Impairment

The 645 patients with nocturia who were recruited to two clinical trials (N4) [21] had a mean baseline overall work impairment of 24 %, and greater disease severity was associated with greater work impairment: the subgroup with four night-time voids (N4c) [21] had mean work impairment of 30 %, the subgroup with five or more voids (N4d) [21] had mean work impairment of 39 %. For 2244 patients with nocturia recruited via their physician to an international cross-sectional real-world survey (N5) [22], mean overall work impairment was reported as 29 %, and greater disease severity was associated with greater work impairment: the subgroup of females with both nocturia and OAB (N5c) [22] had a mean work impairment of 32.5 %, and the subgroup with four or more night-time voids had a mean work impairment of 35 %. In addition to effects on work productivity impairment, this observational study also reported that a deterioration in a range of outcome measures (utility, HRQoL, disease impact diary) was associated with an increasing number of night-time voids ($p < 0.0001$). For 203 respondents self-reporting less severe nocturia symptoms (mean of 1.8 voids in the previous night) in a Swedish population-based study (N1) [20], mean overall work impairment was reported as 14 % and significantly higher than for a matched control group. A regression analysis estimated an average of an additional 2 % work impairment for each additional night-time void.

Figure 2a shows the ranges of percentage overall work productivity impairment due to each health problem identified in this review, as follows: nocturia (14–39 %), OAB (11–41 %), IBS/constipation (21–51 %), GERD (6–42 %), asthma/allergies (6–40 %), COPD (19–42 %), sleep problems (12–37 %), arthritis (21–69 %), pain (29–64 %), depression (15–43 %) and gout (20–37 %). Work productivity impairment reported by patients with nocturia is broadly in line with that in many other chronic diseases such as GERD, asthma/allergies, sleep problems, OAB and gout, whereas WPAI data for arthritis and pain show higher levels of impairment. Similar results were found for the other three outcome measures included in the WPAI instrument.

The ranges of percentage overall work time missed due to each health problem were as follows: nocturia (2–9 %), OAB (1–6 %), IBS/constipation (2–13 %), GERD (1–9 %), asthma/allergies (2–10 %), COPD (5–7 %), sleep problems (3–12 %), arthritis (5–14 %), pain (5–40 %), depression (5–8 %) and gout (7–23 %).

The ranges of percentage impairment while working due to each health problem were as follows: nocturia (12–32 %), OAB (9–44 %), IBS/constipation (20–40 %), GERD (6–40 %), asthma/allergies (10–35 %), COPD (10–31 %), sleep problems (11–43 %), arthritis (18–49 %), pain (25–87 %), depression (19–35 %) and gout (14–33 %).

The ranges of percentage activity impairment due to each health problem were as follows: nocturia (18–40 %), OAB (29–47 %), IBS/constipation (32–57 %), GERD (8–45 %), asthma/allergies (6–50 %), COPD (13–65 %), sleep problems (18–62 %), arthritis (23–59 %), pain (38–71 %), depression (27 %) and gout (29–54 %).

Figure 2b shows disease area WPAI estimates, where study level mean WPAI data are pooled and weighted by study size only, plotted within the observed range for each disease area to show how these compare within and across disease areas. This analysis shows that work impairment among patients with nocturia is estimated to be somewhat central within the range of disease areas included in this

[4] These studies are indicated in Tables 2 and 3.

Table 2 Work productivity and activity impairment cohort studies of chronic disease conditions (among men and women of working age)

Study condition	Study ID [reference]	Quality assessment[a]	Sample size	Mean age (year)	Sex (% male)	Country	Primary condition	WPAI measures			
								% work time missed due to problem	% impairment while working due to problem	% overall work impairment due to problem	% activity impairment due to problem
Nocturia	N4 [21][b]	2–0–0	645	60	60	USA, CAN	Nocturia (any severity)	2.7	22.1	23.7	33.7
	N4a		352				Subgroup: nocturia (2<3)	2.4	21	22	33
	N4b		209				Subgroup: nocturia (3<4)	2.4	23	24	34
	N4c		67				Subgroup: nocturia (4<5)	9	27	30	40
	N4d		15				Subgroup: nocturia (≥5)	7	32	39	37
	N5 [22]	1–0–0	2244		59	USA, FRA, GER, SP, UK	Nocturia (all)	3.4	28.6	29	38.3
	N5a		576		45		Subgroup: nocturia only	1	26.4	27.2	37.5
	N5b		1058		100		Subgroup: nocturia + BPH/OAB males	5.2	28.2	27.5	37.4
	N5c		608		0		Subgroup: nocturia + OAB females	3.5	31.5	32.5	40.3
OAB	OAB3 [25]	2–0–0	85	57	45	KOR	OAB	0.6	17.6	17.3	34.2
	OAB5 [26]	2–0–0	61	58	0	HUN	OAB	0.04	43.6	41.0	47.2
	OAB8a [27]	3–2–0	700	58	31	USA, SWE, ITA, GER, SP, ENG	OAB + continent	3	22	23	29
	OAB8b [27]		907	63	17		OAB + incontinent	6	31	33	41

Table 2 continued

Study condition	Study ID [reference]	Quality assessment[a]	Sample size	Mean age (year)	Sex (% male)	Country	Primary condition	WPAI measures			
								% work time missed due to problem	% impairment while working due to problem	% overall work impairment due to problem	% activity impairment due to problem
IBS	IBS3 [30][b]	1–0–0	1555	44	10	USA	IBS + constipation	3	33.4	35.1	40
	IBS10 [39]	2–1–0	376	32.8	25	DEN	IBS	–	20	20	30
	IBS11 [34]	2–0–0	878	50	10	ITA	Constipation	–	19.7	24.7	–
	IBS13 [35]	2–0–0	921	46	15	CAN	IBS + constipation	6	31	34	37
	IBS14 [36][b]	1–0–0	1363	41	0	INT	IBS + constipation	5.4	40.4	40.4	48.3
	IBS17 [37]	2–0–0	135	45	9	USA	IBS	4.4	32.4	34.2	41.1
	IBS24 [40]	2–1–0	112	41.7	14	ITA	IBS + constipation	3.1	27.7	27.6	41.1
	IBS25 [41]	2–0–0	104	45.4	7	UK	IBS + constipation	8.4	47.9	51.1	56.8
GERD	G4 [43]	2–0–0	716	46	–	FRA	GERD	–	–	31.4	32.6
	G8 [44]	1–0–0	1003	50	32	USA	GERD	1	5.8	6.1	7.6
	G11 [45]	2–0–0	153	50	47.5	CAN	GERD	–	–	16	21
	G12 [46]	2–0–0	2678	52–60	40–47	GER, GRE, NOR, SP, SWE, UK	GERD	2–9	10–20	–	15–26
	G13 [47]	2–0–0	249	49	44	GER	GERD	–	17.6	–	–
	G19 [48][c]	1–2–0	7982	47	46	USA	GERD + sleep problems	7.2	29.7	23.6	44.6
	G20 [49]	1–0–0	115	45	42	USA	GERD (severe night-time symptoms)	–	–	20	–
	G28 [51][b]	1–0–0	61	–	–	SWE	GERD	–	–	13	26
	G31 [52]	2–0–0	135	–	–	SWE	GERD	–	–	23	30
	G40 [53]	1–0–0	8 studies	–	–	Multi	GERD	1–7	6–40	6–42	–
	G43 [54]	2–0–0	887	51	47	GRE	GERD	–	–	–	37.4

Table 2 continued

Study condition	Study ID [reference]	Quality assessment[a]	Sample size	Mean age (year)	Sex (% male)	Country	Primary condition	WPAI measures			
								% work time missed due to problem	% impairment while working due to problem	% overall work impairment due to problem	% activity impairment due to problem
Asthma and Allergies	A2 [55]	2–2–0	785	–	–	SWE, DEN, NOR	Asthma	2.4	10.1	–	13.2
	A3 [56]	1–0–0	3052	39	45	FRA	Rhinitis (all groups)	–	–	20–40	20–50
	A5 [57]	2–0–0	1186	–	–	USA	Asthma	–	–	21.4	32.1
	A6 [58]	1–0–0	2529	–	–	USA	Asthma (all)	–	–	14–27	21–41
	A13 [60]	1–0–0	360	40	23	USA	Asthma (uncontrolled)	4.5	12.7	16.9	19.1
	A14 [61]	2–2–0	1875	47.3	36	FRA, GER, ITA, SP, UK	Asthma (uncontrolled)	10.4	32.5	–	48.8
	A16 [62]	1–0–0	2878	46	34	USA	Asthma	–	–	–	26
	A33 [63][b]	1–0–0	422	33	37	USA	Allergic rhinitis	1.7	35	35.7	40.3
	A36 [64]	1–0–0	56	–	–	USA	Chronic rhinosinusitis	–	–	38.3	–
	A39 [65]	1–0–0	832	44	35	USA	Asthma	–	–	6–15	6–16
COPD	C1 [66]	2–2–0	970	63	–	USA	COPD	7	30.7	34	47
	C2 [67]	2–2–0	297	>65	–	USA	COPD	–	12.6	19.3	23.9
	C3 [68]	2–2–0	112	40–64	–	USA	COPD	–	18.9	20.5	23.5
	C4 [69]	1–0–0	2426	45–67	–	BRA, CHI, GER, TUR, USA, UK	COPD	4.7	10	–	13
	C5 [70]	1–0–0	3617	>40	–	USA	COPD (all)	–	18–23	21–25	49–52
	C6 [71]	2–0–0	314	68	51	USA	COPD	–	–	31.1–42.4	55.6–64.6
	C8 [72][b]	1–0–0	238	61	70	INT	COPD	–	–	21.1	28
Sleep	S2 [75][c]	1–2–0	2388	50.5	38	USA	Insomnia	10.7	29.2	24.2	47.6
	S3 [73]	2–2–0	1119	48.7	38.5	USA	Sleep problems (depression/anxiety)	10.4–12.2	40.9–42.7	33.6–37.4	59.6–61.5
	S11 [74]	2–2–0	2115	53.3	39	USA	Sleep problems	2.5	10.8	12	18.3

Table 2 continued

Study condition	Study ID [reference]	Quality assessment[a]	Sample size	Mean age (year)	Sex (% male)	Country	Primary condition	WPAI measures			
								% work time missed due to problem	% impairment while working due to problem	% overall work impairment due to problem	% activity impairment due to problem
Arthritis	ART2 [76][bc]	1–0–0	197	–	–	HK, IND, MAL, PHI, TAI, KOR, THAI	RA	10.6	48.9	52.3	58.6
	ART3 [77][c]	2–0–0	150	48.1	28	UK	RA	8.7	24	–	33.3
	ART4 [78][c]	1–2–0	62	47	45	NETH	RA	–	20	–	–
	ART5 [79]	2–0–0	1739	64	37	FRA, GER, ITA, SP, UK	OA	–	–	24.3–68.6	–
	ART6 [80]	2–0–0	90	50	29	ARG	RA	14	38.4	45	42
	ART9 [81][c]	2–2–0	2173	52	42	USA	OA pain	8.1	30.7	34.4	38.3
	ART10 [82][c]	2–2–0	4876	–	45	USA	OA (mild–severe)	4.9–14.3	18.3–41.2	21–47.4	23–49.3
	ART12 [83]	2–0–0	204	46.6	28	USA	RA	9.9	39.7	43.2	56.2
	ART20 [88][b]	1–0–0	834	48.4	16.8	Central, Eastern EUR	RA	11.8	33.8	38.2	41.3
	ART21 [84]	2–0–0	356	60	20	AUS	RA	7.7	27.8	–	35.9
	ART22 [85][b]	1–0–0	190	41	82	INT	AS	9	41.7	43.9	–
	ART27 [86]	2–0–0	236	–	–	UK	Psoriatic arthritis	14	39	46	–
	ART33 [87]	2–0–0	150	52	–	CAN	RA	8.7	24	29.1	33.3

Table 2 continued

Study condition	Study ID [reference]	Quality assessment[a]	Sample size	Mean age (year)	Sex (% male)	Country	Primary condition	WPAI measures			
								% work time missed due to problem	% impairment while working due to problem	% overall work impairment due to problem	% activity impairment due to problem
Pain	P6 [89]	2–0–0	493	53	38	USA, CAN, GER, UK	Chronic (non-cancer) pain (+ opioid-induced constipation)	8.9	32.2	29	38.4
	P10 [90]	1–0–0	193	33	0	PR	Pain symptoms	13	65	64	60
	P12 [91]	1–0–0	720	–	–	SWE	Pain (arthritis)	–	25	–	33
	P15 [92]	2–0–0	47	48.1	39	DEN	Chronic (non-cancer) pain	19.4	51.1	41	71
	P16 [93]	1–0–0	5039	–	–	SP	Pain	12.13	25.1	–	–
	P17 [94]	2–2–0	–	–	–	UK, FRA, SP, GER, ITA	Neuropathic/chronic pain	24–39.8	66.7–86.5	–	–
	P32 [95]	1–2–0	785	–	–	JAP	Chronic pain	4.74	30.2	31.7	–
	P33 [96]	2–2–0	191	42	43	JAP	Depressed with pain	13.7	46.4	51.7	55.3
	P34 [97]	2–0–0	104	–	–	USA	Chronic pain	–	–	36.1	55
Depression	D1 [98]	1–0–0	17,820	–	–	JAP	Depression	–	–	14.8–33.3	–
	D4 [99]	1–0–0	740	42.5	25	USA	Depression	8.2	35.2	37.8	–
	D9 [100]	1–0–0	308	61.8	28.6	USA	Caregiver strain	4.9	18.5	20.1	27.2
	D22 [101][c]	1–0–0	1928	–	–	USA	Depression	–	–	34–43	–
Gout	G03 [103]	1–0–0	320	61	81	USA, FRA, GER, UK	Gout	6.8–8.7	14.1–33.3	19.8–36.6	29–54.2

ARG Argentina, *AS* ankylosing spondylitis, *AUS* Austria, *BPA* benign prostatic hyperplasia, *BRA* Brazil, *CAN* Canada, *CHI* China, *COPD* chronic obstructive pulmonary disease, *DEN* Denmark, *ENG* England, *EUR* Europe, *FRA* France, *GER* Germany, *GERD* gastroesophageal reflux disease, *GRE* Greece, *HK* Hong Kong, *HUN* Hungary, *IBS* irritable bowel syndrome, *ID* identification, *IND* India, *INT* International, *ITA* Italy, *JAP* Japan, *KOR* Korea, *MAL* Malaysia, *NETH* Netherlands, *NOR* Norway, *OA* osteoarthritis, *OAB* overactive bladder, *PHI* Philippines, *PR* Puerto Rico, *RA* rheumatoid arthritis, *SP* Spain, *SWE* Sweden, *TAI* Taiwan, *THAI* Thailand, *TUR* Turkey, *UK* United Kingdom, *USA* United States of America, *WPAI* Work Productivity and Activity Impairment instrument, *WPAI: GH* Work Productivity and Activity Impairment instrument—general health version

[a] Newcastle–Ottawa scale for cohort studies, scored on three categories: selection (out of four); comparability (out of two); outcome (out of three)

[b] WPAI data collected at baseline (pre-intervention) in a randomised controlled trial

[c] Study states WPAI-GH instrument is used

Table 3 Work productivity and activity impairment studies of chronic disease conditions with concurrent control groups (population-based matched case-control studies among men and women of working age)

Study condition	Study ID [reference]	Quality assessment[a]	Sample size	Primary condition	Country	WPAI measures					
						% work time missed due to problem	% impairment while working due to problem	% overall work impairment due to problem	Difference in % overall work impairment, *p* value	% activity impairment due to problem	Difference in % activity impairment, *p* value
Nocturia	N1a [20]	4–2–1	203	Nocturia	SWE	**1.6**	**12.3**	**13.8**	<0.001	**18.1**	<0.001
	N1b [20]		80	Control		4.6	3.5	4.6		5.2	
OAB	OAB1a [23]	2–2–1	1434	OAB	SWE, ITA, CAN, GER, UK	**5.2**	**8.8**	**11**	<0.001	**–**	–
	OAB1b [23]		1434	Control		3.4	3.6	5.3		–	
	OAB2a [24][b]	2–2–1	2323	OAB	USA	**–**	**–**	**20**	<0.001	**–**	–
	OAB2b [24][b]		3472	Control		–	–	5.5		–	
IBS/constipation	IBS1a [28][b]	3–2–1	2696	IBS + constipation	GER, FRA, UK	**9**	**25.3**	**27.2**	<0.001	**38.9**	<0.001
	IBS1b [28][b]		23,772	Control		4.6	12.7	13.5		21.3	
	IBS2a [29][b]	3–2–1	3895	IBS + constipation	USA	**9.9**	**28.3**	**30.8**	<0.001	**42**	<0.001
	IBS2b [29][b]		36,835	Control		3.5	12.6	13.7		20.8	
	IBS7a [31]	3–2–1	720	IBS	USA	**1.7**	**21**	**21.1**	<0.001	**–**	–
	IBS7b [31]		1056	Control		0.4	6	6.1		–	
	IBS8a [32][b]	3–2–1	83	IBS + constipation	FRA	**13.2**	**26**	**34.2**	0.021	**40**	0.0001
	IBS8b [32][b]		249	Control		8.7	13.9	19.7		25.5	
	IBS8c [32][b]		201	IBS + constipation	UK	**6.7**	**26.5**	**29.5**	0.024	**36.6**	0.0002
	IBS8d [32][b]		603	Control		6.3	17.4	21.9		27.2	
	IBS8e [32][b]		109	IBS + constipation	ITA	**5.5**	**24.8**	**28.1**	0.057	**31.8**	0.0553
	IBS8f [32][b]		327	Control		2.3	19.8	20.9		25.8	
	IBS9a [33][b]	3–2–1	789	IBS + constipation	USA	**–**	**31.7**	**35.5**	<0.01	**45.8**	<0.01
	IBS9b [33][b]		789	Control		–	21.4	25.3		33.0	
	IBS23a [38][b]	3–2–1	1430	Constipation (chronic)	USA	**9.1**	**29.5**	**33.7**	<0.01	**46.6**	<0.01
	IBS23b [38][b]		1430	Control		5.2	19.1	21.6		33.9	

Table 3 continued

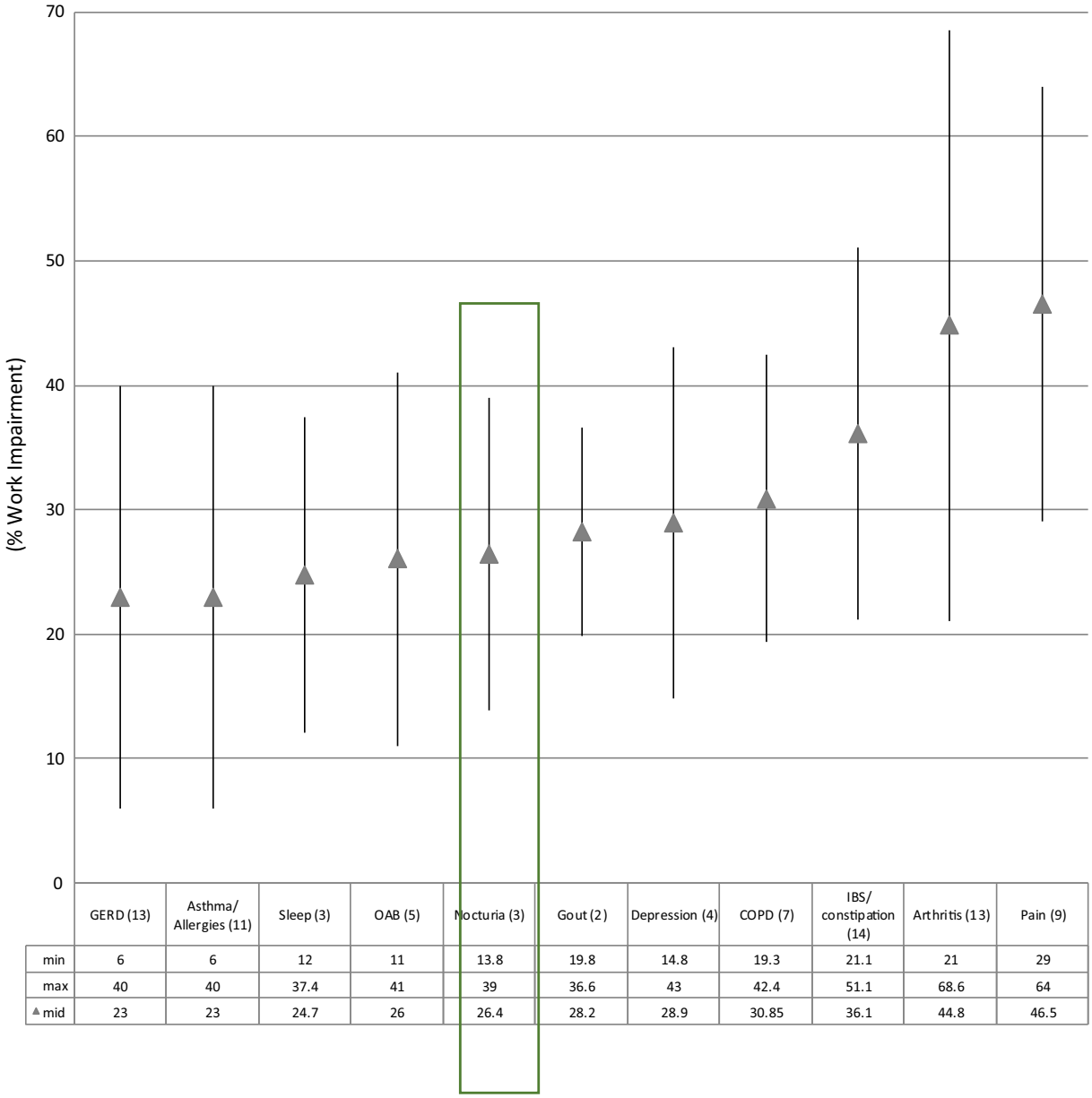
Study condition	Study ID [reference]	Quality assessment[a]	Sample size	Primary condition	Country	WPAI measures					
						% work time missed due to problem	% impairment while working due to problem	% overall work impairment due to problem	Difference in % overall work impairment, *p* value	% activity impairment due to problem	Difference in % activity impairment, *p* value
GERD	G1a [42]	3–2–1	337	GERD (nocturnal heartburn)	SP	–	–	**26.6**	<0.05	**40.2**	<0.05
	G1b [42]		198	GERD (non–nocturnal heartburn)		–	–	**24.9**		**29.6**	
	G1c [42]		198	Control–hypertension		–	–	12.6		22.1	
	G1d [42]		104	Control–depression		–	–	58.6		67	
	G23a [50]	3–2–1	281	GERD	KOR	**1.5**	–	**34.1**	<0.0001	**33.1**	<0.0001
	G23b [50]		728	Control		0.5	–	9.2		9.0	
Asthma and allergies	A11a [59][b]	4–2–2	237	Rhinitis	SP	**4.6**	**23.5**	**26.8**	<0.05	**27.8**	<0.05
	A11b [59][b]		60	Control–diabetes		4.2	15.4	16.7		25.7	
	A11c [59][b]		157	Control–hypertension		2.1	7.3	8.8		19.8	
	A11d [59][b]		162	Control–depression		31.7	49.4	59.5		59.4	
Gout	G01a [102][b]	3–2–1	21,663	Gout (+ hypertension)	USA	–	–	**23.3**	<0.05	–	–
	G01b [102][b]		1023	Control–hypertension		–	–	17.4		–	

Bold values indicate cases and non-bold values indicate controls

CAN Canada, *FRA* France, *GER* Germany, *GERD* gastroesophageal reflux disease, *IBS* irritable bowel syndrome, *ID* identification, *ITA* Italy, *KOR* Korea, *OAB* overactive bladder, *SP* Spain, *SWE* Sweden, *UK* United Kingdom, *USA* United States of America, *WPAI* Work Productivity and Activity Impairment instrument, *WPAI: GH* Work Productivity and Activity Impairment instrument—general health version

[a] Newcastle–Ottawa scale for cohort studies, scored on three categories: selection (out of four); comparability (out of two); exposure (out of three)

[b] Study states WPAI-GH instrument is used



	GERD (13)	Asthma/ Allergies (11)	Sleep (3)	OAB (5)	Nocturia (3)	Gout (2)	Depression (4)	COPD (7)	IBS/ constipation (14)	Arthritis (13)	Pain (9)
min	6	6	12	11	13.8	19.8	14.8	19.3	21.1	21	29
max	40	40	37.4	41	39	36.6	43	42.4	51.1	68.6	64
▲mid	23	23	24.7	26	26.4	28.2	28.9	30.85	36.1	44.8	46.5

Fig. 2 Range of percentage overall work impairment due to health problem found in multiple studies for chronic disease conditions using the Work Productivity and Activity Impairment instrument. *COPD* chronic obstructive pulmonary disease, *GERD* gastroesophageal reflux disease, *IBS* irritable bowel syndrome *OAB* overactive bladder

review: higher than five disease areas (GERD, asthma/allergies, sleep problems, OAB and gout) and lower than five disease areas (depression, IBS/constipation, COPD, arthritis and pain conditions).

When organising WPAI results for all 113 groups included in this review by descending rank order of mean percentage overall work and activity impairment, nocturia studies (all severities) rank around the middle of this full dataset (Figs. 3, 4). The most severe subgroups (highest number of voids per night) from nocturia studies N4d [21] and N5c [22] rank 15th and 35th, respectively, of 113.

4 Discussion

4.1 Summary of Main Results

Work and activity impairment has been studied for longer, in more studies and among more patients within the 12 common chronic conditions used as comparators than in studies on nocturia. Analysis of the ranges of reported impairment due to these conditions, pooled estimates for each disease area, and ranking analyses all find that patients with nocturia report neither the highest nor the

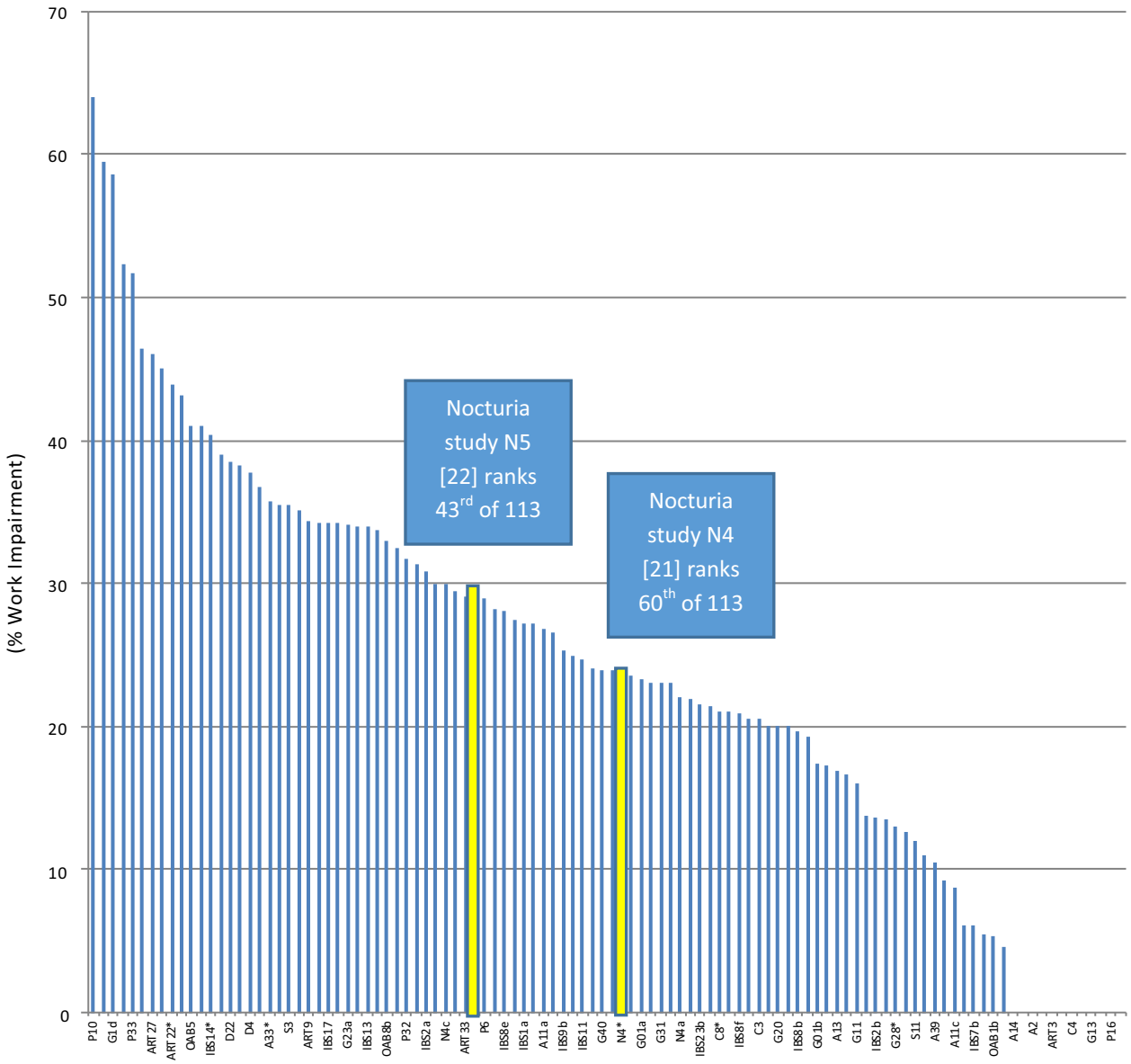


Fig. 3 Mean percentage overall work impairment due to health problem as measured by the Work Productivity and Activity Impairment instrument: full dataset in descending rank order

lowest work and activity impairment within this dataset. Overall work impairment for nocturia identified in this review ranges from 14 to 39 %. The pooled estimate for the three nocturia studies included is 27 % work impairment. Nocturia studies rank very centrally within this dataset: nocturia study N5 [22] ranks 43rd of 113 studies ordered by work impairment, and nocturia study N4 [21] ranks 60th of 113.

Comparing the ranges of overall work impairment results across chronic diseases shows that the upper estimates of the range identified for each study in this review is very similar for a number of disease conditions. The results of studies in patients with seven of the disease conditions included in this review (OAB, GERD, asthma/allergies, COPD, sleep problems, depression, gout) are very similar to those in patients with nocturia, with all reporting an upper estimate of mean percentage overall work impairment around 40 %. Lower estimates of the range of overall work impairment reported for these diseases are also very similar, except for asthma/allergies (6–40 %), which includes patients with much lower impairment, and IBS/constipation (21–51 %) and gout (20–37 %), which have higher lower ranges. Studies of patients with arthritis and pain conditions report higher ranges of overall work impairment than those with other chronic disease conditions in this review: 21–69 % and 29–64 %, respectively.

The WPAI measure of overall work impairment is an aggregation of work time missed (absenteeism) and

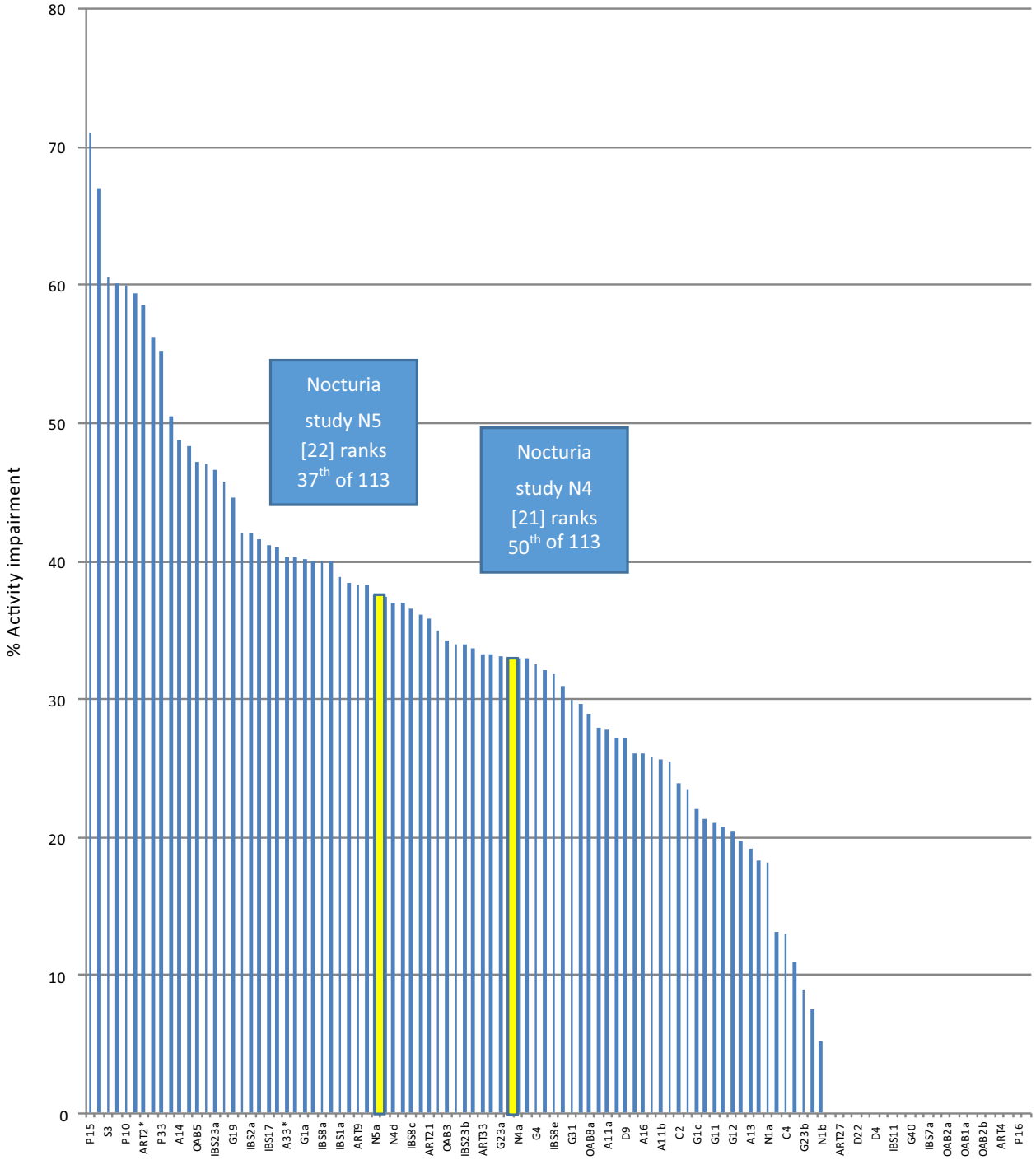


Fig. 4 Mean percentage activity impairment due to health problem as measured by the Work Productivity and Activity Impairment instrument: full dataset in descending rank order

impairment while working (presenteeism), hence similar patterns of impairment across the diseases included in this review are also found for the WPAI metrics of absenteeism and presenteeism.

All three nocturia studies identified in this review measured activity impairment, which can also be reported among non-working participants. Three nocturia studies found a range of mean percentage activity impairment: 33–40 % [21], 37–40 % [22] and 18 % [20]. The ranges identified for mean percentage activity impairment for each health problem are considerably wider than for other WPAI outcome measures. For example, activity impairment among studies of asthma/allergies ranged from 6 to 50 %. This increased variability may be due to the inclusion in

some studies of retired (non-working) participants who may be older and have more severe disease and co-morbidities.

4.2 Overall Completeness and Applicability of Evidence

This review aimed to characterise the burden of nocturia by considering published data from studies of patients with nocturia and patients with any of 12 other common chronic conditions. The consolidated descriptive presentation of the available evidence in this area provides context for this comparison. We identified 84 studies, with an aggregate of more than 128,000 patients with the target disease areas having completed the WPAI instrument and 113 patient groups containing at least one of the WPAI outcome measures. This constitutes a reasonable body of evidence with which to meet the research objectives.

Meta-analyses of WPAI data from these studies were problematic, since study-level data from the publications were insufficient to enable informed judgements to control for relevant patient-, disease- and job-related covariates; no patient-level data were available. Pooled estimates of mean work impairment were estimated for each disease area, adjusting only for the size of studies contributing to each pool. Comparison of baseline characteristics at the study level was restricted to age, percentage male/female and study setting (single country vs. international study); meta-analyses adjusting for these and other potentially relevant parameters would require more information than could be obtained from the review of published literature.

We based our selection of chronic disease conditions to compare with nocturia and include in the review on clinical judgement of appropriateness and data manageability; clearly, other diseases could be added to the review where suitable. It may be appropriate to consider comparing the extent of impairment in other areas in which WPAI studies have been conducted, including hypertension, women's health, dermatology, diabetes, eye diseases and mental health disorders.

This review of work productivity and activity impairment was restricted to studies focused on one instrument: the WPAI. We selected this based on the authors' experience that the WPAI is the most widely used across a large range of disease areas and has been subject to rigorous validation in many contexts in many countries. The review could, of course, be extended to include other measures of work productivity and activity impairment, but it may not be possible to combine the results of different measures and they may need to be presented independently. A wider review of other measures of the burden of chronic diseases, such as disease-specific and generic HRQoL measures could also be conducted. This review did extract HRQoL data from the identified studies to facilitate further analyses in this area.

The use of work productivity instruments, such as the WPAI, within both intervention and observational studies appears to be increasing, perhaps as healthcare decision makers and policy makers are attaching more weight to these types of measures of disease burden. Generally, productivity measures remain as supportive evidence in most health technology assessments of new medicines and technologies, although a few systems now formally incorporate them.

Further productivity data among a wider range of patients with nocturia will further characterise the burden of this condition and increase comparability with other diseases. Further burden-of-illness type studies are needed to contribute to this evidence base, but studies should consider the quality assessment of studies included in this review and which study design aspects may be enhanced to deliver better quality scores on the Newcastle–Ottawa scale [18] or similar. Well-conducted case–control studies that better document non-responder characteristics and the handling of missing data would be valuable.

4.3 Potential Biases in the Review Process

Two main potential biases might affect the findings of this review. First, confounding factors, such as age, disease severity and co-morbidities, may be unevenly distributed across studies, countries and disease groupings. Second, participants in WPAI studies may be systematically different to non-participants with the chronic health problems, leaving the review at risk of selection bias. Studies collecting WPAI data as part of a randomised controlled trial tended to report greater work and activity impairment, although differences were not formally tested.

5 Conclusion

Although the data published for nocturia are still limited and meta-analyses are somewhat constrained by the study-level information available from published sources, the overall work productivity impairment as a result of nocturia would appear to be substantial and similar to that of several other more frequently researched common chronic diseases. Greater awareness of the burden of nocturia, a highly bothersome and prevalent condition, will help policy makers and healthcare decision makers provide appropriate management of nocturia.

Acknowledgments Paul Miller and Harry Hill conducted the searches, data extraction and data syntheses and contributed to drafting the manuscript. Fredrik Andersson designed the project and contributed to drafting the manuscript.

Compliance with Ethical Standards

Funding Paul Miller and Harry Hill received funding from Ferring Pharmaceuticals to undertake this work.

Conflict of interest Paul Miller has received funding from Ferring Pharmaceuticals for conference travel. Fredrik Andersson is an employee of Ferring Pharmaceuticals, which markets treatments for nocturia.

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