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ORIGINAL RESEARCH

Validity of Prescription-Defined and Hospital-Diagnosed Hypertension Compared with Self-Reported Hypertension in Denmark

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Purpose: Hypertension is an important risk factor in cardio-epidemiological research, but data quality remains a concern. We validated different registry-based definitions of hypertension.

Patients and Methods: The cohort included all first-time responders of the Danish National Health Surveys (2010, 2013, or 2017). Prescription-defined hypertension was defined as ≥1 or ≥2 filled prescriptions of antihypertensive specific drugs in ≥1 or ≥2 different antihypertensive drug classes within 90, 180, or 365 days before survey response. Hospital-diagnosed hypertension was defined from hypertension diagnoses within five years before the survey response. Considering self-reported hypertension as the reference, we calculated the positive predictive value (PPV), the negative predictive value (NVP), the sensitivity, and the specificity of prescription-defined and hospital-diagnosed hypertension.

Results: Among 442,490 survey responders, 127,247 (29%) had self-reported hypertension. For prescription-defined hypertension with 365-day lookback, the PPV was highest for ≥2 prescriptions in ≥2 drug classes (94%) and lowest for ≥1 prescription in ≥1 drug class (85%). The NPV was highest for ≥1 prescription in ≥2 drug classes (94%) and lowest for ≥1 prescription in ≥2 drug classes (80%). The sensitivity was highest for ≥1 prescription in ≥1 drug class (79%) and lowest for ≥2 prescriptions in ≥2 drug classes (30%). The specificity was ≥94% for all algorithms. The PPV and specificity did not change noteworthy with length of lookback period, whereas the NPV and the sensitivity generally were higher for longer lookback. The algorithm ≥1 prescription in ≥2 drug classes with 365-day lookback was among the best balanced across all measures of validity (PPV=88%, NPV=94%, sensitivity=75%, specificity=96%). For hospital-diagnosed hypertension, the PPV was 90%, the NPV was 76%, the sensitivity was 22%, and the specificity was 99%.

Conclusion: Compared with self-reported hypertension, the algorithms for prescription-defined and hospital-diagnosed hypertension had high predictive values and specificity, but low sensitivity.

Keywords: epidemiologic studies, epidemiology, hypertension, predictive value of tests, sensitivity and specificity, validation study

Introduction

Registry-based research relies on accurate information on co-variables to account for baseline differences in risk factors between exposure groups.[1] Hypertension is a common risk factor for cardiovascular disease[2] and therefore an important co-variable to consider in cardiovascular research. Hospital registries do not identify persons with hypertension solely treated by their general practitioner.[3] Hospital data is therefore often supplemented with prescription data to identify hypertension. Prescription-defined hypertension is commonly defined as two or more filled prescriptions for two or more different antihypertensive drug classes.[4] However, there are concerns that this approach misclassifies persons on antihypertensive monotherapy as not having hypertension and persons using antihypertensive drugs solely for other conditions, in particular congestive heart failure, as having hypertension. We, therefore, examined the validity of prescription-defined and hospital-diagnosed hypertension compared with self-reported hypertension.

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Materials and Methods

Setting

The Danish healthcare system provides free, tax-financed treatment at general practitioners and hospitals and partial reimbursement for prescription drug expenses to all Danish residents.[5] Danish residents receive at birth or upon immigration a unique Civil Personal Registration number that functions as a personal identifier across all health services in Denmark, thereby allowing individual-level linkage between Danish health registries and virtually complete long-term follow-up with accurate censoring at death or emigration.[6]

Study Population

We included all first-time responders of the Danish National Health Surveys in 2010, 2013, or 2017 without missing information on self-reported hypertension. These surveys consisted of at least 50 questions on lifestyle and socioeconomic position and were in each survey year sent to six (one national and five regional) mutually exclusive random samples among the adult (16 years of age or older) Danish population.[7] The survey response rates were 60% in 2010, 54% in 2013, and 59% in 2017.[7] As the surveys did not contain the exact date of completion, we defined the date of completion as 1 May in the survey year because the surveys were conducted between the end of January and the beginning of May in each survey year.[7]

Hypertension Definitions

Self-reported hypertension was defined as self-reported current or previous hypertension. Supplementary Table 1 presents the codes used to identify prescription-defined and hospital-diagnosed hypertension. Prescription-defined hypertension was defined using different algorithms based on the minimum number (≥1 or ≥2) of filled prescriptions of the same drug (eg, enalapril or amlodipine) in the minimum number (≥1 or ≥2) of different antihypertensive drug classes (eg, angiotensin-converting enzyme inhibitors or calcium channel blockers) within a specific lookback period (90, 180, or 365 days). All algorithms were analyzed using both antihypertensive unspecific and specific drugs. Antihypertensive unspecific drugs were defined as any drug within the antihypertensive drug classes alfa-blockers, beta-blockers, calcium channel blockers, renin-angiotensin-aldosterone inhibitors (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and renin inhibitors), non-loop diuretics, and vasodilators (thiazide, pyrimidine, and guanidine derivatives; peripheral vasodilators; and vasoprotectives). Antihypertensive specific drugs included all drugs within the drug classes angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and thiazides, excluding the more heart failure specific drugs (trandolapril, sacubitril/valsartan, and nebivolol). We identified filled prescriptions via the Danish National Prescription Registry, which contains information on all filled prescriptions from Danish community pharmacies since 1995.[8]

Hospital-diagnosed hypertension was defined as a primary or secondary, in or outpatient diagnosis code of hypertension within five years before the survey response. We identified diagnoses via the Danish National Patient Registry, which contains information on inpatient non-psychiatric contacts since 1977, and on inpatient psychiatric, all outpatient, and all emergency room contacts since 1995.[3]

Statistical Analyses

We reported the survey responders' characteristics, morbidities, and drug use via numbers with percentages for categorical variables and medians with interquartile ranges for continuous variables. Using self-reported hypertension as the reference, we calculated the positive predictive value (PPV), the negative predictive value (NPV), the sensitivity (as a measure of completeness), and the specificity of prescription-defined and hospital-diagnosed hypertension. For prescription-defined hypertension, the PPV was calculated as the proportion of self-reported hypertension among individuals with prescription-defined hypertension. The NPV was calculated as the proportion without self-reported hypertension among individuals without prescription-defined hypertension. The sensitivity was calculated as the proportion of prescription-defined hypertension among individuals with self-reported hypertension. The specificity was calculated as the proportion without prescription-defined hypertension among individuals without self-reported hypertension. Similar approaches were used for the hospital-defined hypertension estimates. We performed the analyses in subgroups of

sex and age (16–44, 45–64, or ≥65 years) to test for demographic differences. We used the Wilson Score method to calculate 95% confidence intervals (Cis).[9]

Results

Characteristics of Survey Responders

We identified 471,769 first-time responders of the Danish National Health Surveys in 2010, 2013, or 2017, of which 29,279 (6%) had missing information on self-reported hypertension. Thus, the cohort consisted of 442,490 individuals, among whom 125,509 (28%) had self-reported hypertension, 108,040 (24%) had prescription-defined hypertension (when using the algorithm of ≥1 prescription in ≥2 antihypertensive specific drugs within 365 days before the survey response), and 30,463 (7%) had hospital-diagnosed hypertension. Table 1 presents the characteristics of these individuals at the time of survey response. Among all survey responders, the median age was 53 years (interquartile range, 40–66 years) and 238,247 (54%) were females. The median age increased if the survey responders had self-reported (65 years),

Table 1 Characteristics of First-Time Responders of the Danish National Health Surveys (2010–2017) at the Time of Survey Response According to Self-Reported, Prescription-Defined, and Hospital-Diagnosed Hypertension

Characteristics	All Survey Responders N=442,490	Hypertension		
		Self-Reported N=125,509	Prescription-Defined* N=108,040	Hospital-Diagnosed† N=30,463
Female sex — N (%)	238,247 (53.8)	65,000 (51.8)	55,735 (51.6)	15,925 (52.3)
Age, years — Median (IQR)	53.1 (39.5–65.8)	65.0 (55.4–73.0)	67.6 (59.6–74.9)	69.1 (61.0–76.7)
Smoking — N (%)				
Current	203,203 (45.9)	49,147 (39.2)	40,962 (37.9)	11,090 (36.4)
Former	140,297 (31.7)	50,388 (40.1)	45,985 (42.6)	13,537 (44.4)
Never	93,583 (21.1)	23,644 (18.8)	18,821 (17.4)	5073 (16.7)
Body mass index — N (%)				
<18.5	8322 (1.9)	1424 (1.1)	1242 (1.1)	411 (1.3)
18.5–24.9	201,644 (45.6)	38,637 (30.8)	32,764 (30.3)	8785 (28.8)
25.0–29.9	152,895 (34.6)	50,039 (39.9)	43,249 (40.0)	11,759 (38.6)
≥30	67,417 (15.2)	30,963 (24.7)	26,684 (24.7)	8215 (27.0)
Physical activity — N (%)				
Low	11,094 (2.5)	862 (0.7)	530 (0.5)	141 (0.5)
Moderate	281,272 (63.6)	74,475 (59.3)	63,153 (58.5)	16,012 (52.6)
High	133,584 (30.2)	43,169 (34.4)	37,594 (34.8)	12,098 (39.7)
Alcohol intake — N (%)				
Low	335,587 (75.8)	91,221 (72.7)	78,319 (72.5)	22,393 (72.5)
Moderate or high	89,799 (20.3)	27,018 (21.5)	22,723 (21.0)	5815 (19.1)
Comorbidities — N (%)				
Myocardial infarction	7903 (1.8)	5693 (4.5)	6839 (6.3)	2924 (9.6)
Congestive heart failure	6167 (1.4)	4250 (3.4)	5424 (5.0)	2538 (8.3)
Peripheral vascular disease	6995 (1.6)	4937 (3.9)	5213 (4.8)	2537 (8.3)
Cerebrovascular disease	13,418 (3.0)	8855 (7.1)	8746 (8.1)	4933 (16.2)
Dementia	1383 (0.3)	759 (0.6)	760 (0.7)	464 (1.5)
Chronic pulmonary disease	16,476 (3.7)	7117 (5.7)	6973 (6.5)	3366 (11.0)
Rheumatic disease	5191 (1.2)	2495 (2.0)	2498 (2.3)	1066 (3.5)
Peptic ulcer disease	3677 (0.8)	2048 (1.6)	2038 (1.9)	1021 (3.4)
Mild liver disease	2622 (0.6)	1171 (0.9)	1006 (0.9)	441 (1.4)
Diabetes, no chronic complications	14,855 (3.4)	11,056 (8.8)	11,105 (10.3)	6053 (19.9)
Diabetes, with chronic complications	4198 (0.9)	3339 (2.7)	3441 (3.2)	2068 (6.8)

(*Continued*)

Table 1 (Continued).

Characteristics	All Survey Responders N=442,490	Hypertension		
		Self-Reported N=125,509	Prescription-Defined* N=108,040	Hospital-Diagnosed† N=30,463
Hemi- or paraplegia	343 (0.1)	127 (0.1)	115 (0.1)	59 (0.2)
Renal disease	2641 (0.6)	2102 (1.7)	2105 (1.9)	1327 (4.4)
Moderate or severe liver disease	459 (0.1)	234 (0.2)	226 (0.2)	98 (0.3)
Cancer	21,986 (5.0)	9991 (8.0)	9790 (9.1)	4113 (13.5)
Drug usage — N (%)				
Antiplatelets	34,363 (7.8)	25,167 (20.1)	27,279 (25.2)	10,281 (33.7)
Anticoagulants	10,338 (2.3)	6807 (5.4)	8269 (7.7)	3607 (11.8)
ACE inhibitors	35,216 (8.0)	32,171 (25.6)	34,259 (31.7)	9262 (30.4)
A-II-R blockers	28,302 (6.4)	26,808 (21.4)	27,793 (25.7)	8180 (26.9)
Beta-blockers	30,915 (7.0)	24,918 (19.9)	30,147 (27.9)	9745 (32.0)
Calcium channel blockers	32,378 (7.3)	30,117 (24.0)	31,741 (29.4)	9869 (32.4)
Diuretics	53,646 (12.1)	47,109 (37.5)	50,472 (46.7)	14,541 (47.7)
Statins	50,772 (11.5)	36,006 (28.7)	37,521 (34.7)	12,041 (39.5)
Glucocorticoids	12,353 (2.8)	5240 (4.2)	5149 (4.8)	1755 (5.8)
Opioids	19,220 (4.3)	9641 (7.7)	9451 (8.7)	3816 (12.5)
Paracetamol	29,291 (6.6)	15,413 (12.3)	15,407 (14.3)	5947 (19.5)
Respiratory medications	22,982 (5.2)	9945 (7.9)	9841 (9.1)	3272 (10.7)
Proton pump inhibitors	29,786 (6.7)	15,491 (12.3)	15,552 (14.4)	5944 (19.5)
Antidepressants	26,150 (5.9)	10,776 (8.6)	10,140 (9.4)	3720 (12.2)
Antipsychotics	5093 (1.2)	1835 (1.5)	1697 (1.6)	622 (2.0)
NSAID	32,528 (7.4)	12,846 (10.2)	11,907 (11.0)	3352 (11.0)
Anti-diabetics	19,447 (4.4)	14,337 (11.4)	14,684 (13.6)	5472 (18.0)

Note: The columns may not add to 100% due to missing values. *Hypertension defined by the algorithm ≥1 prescription in ≥2 antihypertensive drug classes ≤365 days before survey response (see elaboration in Table 2). †Hypertension diagnosis within five years before survey response.
Abbreviations: ACE, angiotensin converting enzyme; A-II-R, angiotensin II receptor; NSAID, non-steroidal anti-inflammatory drugs.

prescription-defined (68 years), or hospital-diagnosed (69 years) hypertension. Also, the proportion of survey responders with comorbidities and prescription drug usage increased if they had self-reported, prescription-defined, or hospital-diagnosed hypertension.

Prescription-Defined Hypertension

Table 2 presents the estimates of data validity for the different algorithms used to define prescription-defined hypertension compared with self-reported hypertension and the Supplementary Tables 2 and 3 present their CIs and the numbers used for the calculations. Generally, only minor differences were observed between using antihypertensive specific or unspecific drugs. Below we focus on the algorithms using antihypertensive specific drugs. When using 365-day lookback, the PPV was highest for ≥2 prescriptions in ≥2 drug classes (94%) and lowest for ≥1 prescription in ≥1 drug class (85%). The NPV was highest for ≥1 prescription in ≥2 drug classes (94%) and lowest for ≥1 prescription in ≥2 drug classes (80%). The sensitivity was highest for ≥1 prescription in ≥1 drug class (79%) and lowest for ≥2 prescriptions in ≥2 drug classes (30%). The specificity was ≥94% for all algorithms. Reducing the lookback to 90 or 180 days did not change the PPV or the specificity noteworthy but reduced the NPV and the sensitivity for algorithms requiring ≥2 drug classes.

Balancing all measures of data validity, the algorithm ≥1 prescription in ≥2 drug classes with 365-day lookback was among those that performed best (PPV=88%, NPV=94%, sensitivity=75%, specificity=96%). All estimates were comparable between females and males (Supplementary Table 4). In subgroups of age, the PPV and the sensitivity were highest in elderly persons whereas the NPV and the specificity were highest in younger persons (Supplementary Table 4). To illustrate, in individuals 16–44 versus ≥65 years of age, the PPVs were 79% versus 87%, the NPVs were 94% versus 86%, the sensitivities were 27% versus 88%, and the specificities were 99% versus 85%.

Table 2 Validity of Algorithms for Prescription-Defined Hypertension Compared with Self-Reported Hypertension

Antihypertensive Drug Classes and Lookback Periods	Algorithm for Prescription-Defined Hypertension*			
	≥2 Prescriptions in ≥2 drug Classes	≥2 Prescriptions in ≥1 drug Class	≥1 Prescription in ≥2 drug Classes	≥1 Prescription in ≥1 drug Class
	PPV/NPV; Sens/Spec	PPV/NPV; Sens/Spec	PPV/NPV; Sens/Spec	PPV/NPV; Sens/Spec
90-day lookback				
Unspecified drugs†	91/89; 5/100	92/80; 36/99	87/76; 22/99	84/88; 68/95
Specified drugs‡	89/72; 3/100	94/78; 30/99	86/75; 15/99	87/88; 67/96
180-day lookback				
Unspecified drugs†	93/78; 29/99	93/79; 35/99	87/87; 63/96	87/88; 68/96
Specified drugs‡	94/77; 24/99	93/80; 39/99	88/86; 59/97	86/91; 77/95
365-day lookback				
Unspecified drugs†	93/79; 34/99	93/80; 36/99	85/88; 67/95	84/88; 68/95
Specified drugs‡	94/91; 30/99	93/80; 44/99	88/94; 75/96	85/92; 79/94

Notes: *The algorithms are based on the minimum number of filled prescriptions of the same drug (eg, enalapril or amlodipine) in the minimum number of different antihypertensive drug classes (eg, angiotensin-converting enzyme inhibitors or calcium channel blockers) within the specified lookback period. Eg, to have hypertension according to the ≥2 prescriptions in ≥2 drug classes algorithm when using a 90-day lookback, an individual could have ≥2 prescription fillings for enalapril and ≥2 prescription fillings for amlodipine within 90 days before self-reported hypertension. †Any drug within the antihypertensive drug classes: Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, non-loop diuretics, alfa-blockers, and vasodilators. ‡Antihypertensive specific drugs (ie, excluding heart failure specific drugs): Angiotensin-converting enzyme inhibitors (except trandolapril), angiotensin receptor blockers (except sacubitril/valsartan), beta-blockers (except nebivolol), calcium channel blockers, and thiazides.
Abbreviations: NPV, negative predictive value (%); PPV, positive predictive value (%); Sens, Sensitivity (%); Spec, Specificity (%).

Hospital-Diagnosed Hypertension

For hospital-diagnosed hypertension, the PPV was 90%, the NPV was 76%, the sensitivity was 22%, and the specificity was 99%, when using self-reported hypertension as the reference (Table 3). Again, all estimates were comparable between females and males (Supplementary Table 4). The PPV and the specificity were not noteworthy different according to age subgroups, whereas NPV was highest in younger persons and the sensitivity was highest in elderly persons (Supplementary Table 4). To illustrate, in individuals 16–44 versus ≥65 years of age, the NPVs were 93% versus 54% and the sensitivities were 9% versus 28%.

Table 3 Validity of Hospital-Diagnosed Hypertension Compared with Self-Reported Hypertension

		Self-Reported Hypertension (Reference)		
		Yes	No	
Hospital-diagnosed hypertension	**Yes**	True positives (TP) N=27428	False positives (FP) N=3035	Positive predictive value = TP / (TP + FP) = 90 (90–90)
	No	False negatives (FN) N=98081	True negatives (TN) N=313946	Negative predictive value = TN / (FN + TN) = 76 (76–76)
		Sensitivity = TP / (TP + FN) = 22 (22–22)	Specificity = TN / (FP + TN) = 99 (99–99)	

Note: The validity measures are presented in % (95% confidence interval).

Discussion

Compared with self-reported hypertension, we found an overall high PPV, NPV, and specificity, but low sensitivity, for prescription-defined and hospital-diagnosed hypertension. Among the best algorithms identified for prescription-defined hypertension was ≥1 prescription for ≥2 antihypertensive specific drugs within 365 days, yielding a PPV of 88%, NPV of 94%, sensitivity of 75%, and specificity of 96%. For hospital-diagnosed hypertension, the PPV was 90%, the NPV was 76%, the sensitivity was 22%, and the specificity was 99%.

Previous Literature

Previous studies have compared different definitions of hypertension. The algorithm using ≥2 prescriptions of any unspecific antihypertensive drug within ≥2 antihypertensive drug classes has previously been validated in a Danish cohort of 14,994 individuals aged 16 years or older, among whom 2028 individuals reported taking antihypertensive drugs within a two-week period.[4] Here, the PPV was estimated at 80% when compared with self-reported hypertension.[4] We found even higher PPVs, but also evidence of low sensitivity.

A systematic review of 1201 population-representative studies showed that in high-income Western countries, 10% of females and 11% of males diagnosed with hypertension did not receive antihypertensive treatment.[5] A direct comparison with our finding that 22–30% of individuals with self-reported hypertension did not use antihypertensive monotherapy, is difficult due to different references (diagnosis versus self-reporting).

For hospital-diagnosed hypertension, the PPV has ranged from 88% in males when compared with a filling of an antihypertensive drug,[10] 40–60% when compared with diagnoses in the Occupational Hospitalization Register,[11] and 87% for females, 98% for males, and 94% for children younger than 16 years of age when compared with medical record review.[12,13] Direct comparisons with our study are challenging because of the differences in algorithms and reference groups, but we found a similar high PPV for hospital-diagnosed hypertension when compared with self-reported hypertension.

Limitations

Some limitations should be considered. First, because of the large sample size, it was unfeasible to review the survey responders' medical records to validate self-reported hypertension. If responders of the Danish National Health Survey under or overreported hypertension, the true estimates may differ from those observed when compared with self-reported hypertension. Second, the absence of a precise survey response date (between January and May in each survey year) generates some uncertainty about the period to look for hypertension diagnoses and filled antihypertensive drug prescriptions. However, because people treated for hypertension refill prescriptions for their antihypertensive drugs regularly and because we used a long lookback window for the diagnoses (five years), this limitation is of minor concern. Third, because of potential differences in prescription and coding practices, diagnostics, and reimbursement schemes, our findings might not generalize to earlier calendar periods or other countries. Fourth, the results for prescription defined hypertension may not generalize to patient groups with other indications for one or more antihypertensive classes (eg, congestive heart failure, tachyarrhythmia, ischemic heart disease, or migraine).

Implications

Defining hypertension through health registry data inevitably introduces some degree of misclassification. The preference for high PPV or high sensitivity of hypertension therefore depends on the specific study aims. Our study indicates consistently high PPVs for prescription-defined and hospital-diagnosed hypertension when compared with self-reported hypertension. This observation suggests a potential preference for utilizing prescription or hospital data to define hypertension in prognosis studies of hypertension. Conversely, the low sensitivities of these definitions imply that self-reported hypertension may be more suitable for studies of the incidence or prevalence of hypertension. In cases where self-reported data is unavailable, employing an algorithm for prescription-defined hypertension with a heightened sensitivity is advisable (eg, the algorithm ≥1 prescription in ≥1 antihypertensive drug classes with 365-day lookback).

Conclusion

Compared with self-reported hypertension, prescription-defined and hospital-diagnosed hypertension had high predictive values, but low sensitivities. Hence, using algorithms based on prescription or hospital data to identify hypertension appears valid, but may underestimate the true number of persons with hypertension.

Data Sharing Statement

Data sharing is not applicable to this article as no new data was created or analyzed in this study.

Ethics Statement

The study was approved by the Danish Data Protection Agency (record number: 2015-57-0002) via Aarhus University (record number: 2016-051-000001).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

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