Chapter 8

General discussion

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The principle aim of this thesis was to obtain more insight into the epidemiology of dizziness in older patients, and to provide clinical guidance in the diagnostic approach of older dizzy patients in general practice. In this final chapter the results presented in this thesis will be linked together and put in a wider perspective. Additionally, we present recommendations for further research and clinical practice.

Before reflecting on the results presented in this thesis, we present a summary of the main findings.

Main findings of this thesis

Prevalence, incidence, and clinical characteristics of dizziness in general practice

Almost 10% of persons aged 65 or older visited their general practitioner at least once a year because of dizziness. The incidence rates of all dizziness subtypes increased with age, except for the subtype “vertigo”. Dizziness was more common in women than in men, but this gender difference disappeared in the very old. Living alone, lower level of education, pre-existing cerebrovascular disease, and pre-existing hypertension were independently associated with dizziness (Chapter 2).

Recorded diagnoses by general practitioners

For 39% of the dizzy patients the general practitioners did not specify a diagnosis and recorded a symptom diagnosis as the final diagnosis. Other groups of recorded diagnoses were cardiovascular disease (14%), peripheral vestibular disease (12%), psychiatric disease (6%), and musculoskeletal disease (5%; Chapter 2).

Diagnosing dizziness in primary care: the state of the evidence

Until now, all diagnostic accuracy studies reporting on tests suitable for diagnosing dizziness in primary care used some kind of preselection of patients and were intended to diagnose specific conditions, such as Ménière’s disease or peripheral vestibular dysfunction. All accuracy studies were at least partially conducted in a secondary/tertiary care setting, and almost none of the studies included a spectrum of patients representative of primary care patients. The focus of all accuracy studies was limited to tests for neuro-otological and psychiatric conditions (Chapter 3).
Diagnostic tests for evaluating dizziness in general practice

In a Delphi procedure, an expert panel selected 21 out of 37 diagnostic tests for evaluating dizziness in older patients in general practice. Five diagnostic tests were excluded, although they are recommended by several practice guidelines on dizziness, two diagnostic tests were included, although several guidelines question their diagnostic value, and two other diagnostic tests were included, although they have never been recommended by practice guidelines on dizziness (Chapter 4).

Contributory causes of dizziness in older patients in general practice

Application of the selected 21 diagnostic tests, followed by independent review by a multidisciplinary panel, resulted in major and minor contributory causes of dizziness. Cardiovascular disease was considered to be the most common major contributory cause of dizziness in older dizzy patients in general practice (57%), followed by peripheral vestibular disease (14%), and psychiatric disease (10%). In a quarter of all dizzy patients, an adverse drug effect was considered to be a contributory cause of dizziness. Sixty-two percent of the patients were assigned more than one contributory cause of dizziness (Chapter 5).

Diagnostic subtypes/profiles of dizziness in general practice

According to a multidisciplinary panel, presyncope was the most common dizziness subtype (69%), followed by vertigo (41%), disequilibrium (40%), and other dizziness (2%; Chapter 5).

Using principal component analysis of findings from history, physical examination and additional diagnostic tests, six diagnostic profiles of dizziness could be identified: “frailty”, “psychological”, “cardiovascular”, “presyncope”, “non-specific dizziness”, and “ENT”. Sixty-seven percent of the patients scored on more than one dizziness profile (Chapter 6).

Predicting anxiety and depression in older dizzy patients in general practice

An anxiety and/or depressive disorder was present in 22% of older dizzy patients in general practice. Dizziness-related disability was a strong diagnostic indicator of anxiety and/or depression. Other diagnostic indicators of anxiety and/or depression were accompanying fear and a history of depression (associated with an increased odds), and tinnitus and rotational dizziness (associated with a decreased odds; Chapter 7).
Overall, the results presented in this thesis confirm several existing insights, both on the epidemiology of dizziness (e.g., dizziness is very common among older persons, dizziness increases with age, and dizziness is more common in women than in men) and on diagnosing dizziness (e.g., history taking is the key diagnostic tool when evaluating dizziness, and dizziness is often multi-causal, especially in older patients). Additionally, our results provide new information, both on the epidemiology of dizziness (e.g., gender differences with regard to prevalence and incidence rate are absent in the oldest dizzy patients, living alone is independently associated with dizziness, and Dutch general practitioners often record a symptom diagnosis as the final diagnosis of dizziness) and on diagnosing dizziness (e.g., cardiovascular disease - and not vestibular disease - is the main contributory cause of dizziness in older primary care patients, adverse drug effect is a common contributory cause of dizziness, and dizziness-related disability is a strong diagnostic indicator of anxiety and depression in older dizzy patients).

Expert opinion as methodological instrument: learning more about the elephant or just increasing the number of blind men?

In this thesis, expert opinion as a methodological instrument played a key role. In the Delphi procedure (Chapter 4) we used the opinion of experts from eight different medical disciplines (i.e. cardiology, ENT, general practice, geriatric medicine, internal medicine, neurology, nursing home medicine, and rehabilitation medicine) to select diagnostic tests for the evaluation of dizziness, because - as evidence is scarce and guidelines are contradictory - we wanted to maximally justify our applied diagnostic evaluation. In the cross-sectional diagnostic study (Chapter 5) we used the opinion of clinicians from three different medical disciplines (i.e. general practice, geriatric medicine, and nursing home medicine) to interpret the test results, in order to counterbalance investigator bias. Until now, no previous study on dizziness used expert opinion for the selection of diagnostic tests, and only two studies used multiple rating for the interpretation of test results (Kroenke et al.: a general internist, a neurologist, and a neuro-opthalmologist; Sloane and Baloh: a general practitioner and a neurologist).

In the cross-sectional diagnostic study (Chapter 5) we referred to the story of the “blind men and the elephant”. In this Indian tale, a group of blind men touch an elephant in order to determine what it is like. Each of the men touches a different part of the elephant, and when they compare their findings, they are in complete...
disagreement. The tale is used to illustrate that reality depends upon one’s perspective. As Sloane previously stated, this phenomenon also occurs in the field of dizziness: investigators tend to diagnose conditions that they know about or are interested in. Examples of this phenomenon are the study of Colledge et al. (geriatric perspective; the authors report a very high prevalence of cervical spondylosis as a cause of dizziness [66%]), and Lawson et al. (cardiovascular perspective; unusually high prevalence of carotid sinus hypersensitivity as a cause of dizziness [34%]). The key question is: did the application of expert opinion in our study actually widen the perspective on diagnosing dizziness? Or, using the Indian tale, did we just increase the number of blind men without learning more about the elephant?

In our opinion, we definitely learned more about this intriguing elephant dizziness actually is. First of all, our efforts to collect and assess all empirical evidence (Chapter 3) and to create a “learning document” for the members of the expert panel (Chapter 4) facilitated the panel to improve their expertise (i.e. “education of the blind men”). Furthermore, the Delphi procedure itself (Chapter 4) enabled the panel to share their expertise anonymously, to learn from other experts, and - if necessary - to change their opinion (i.e. “communication between the blind men”). Finally, we used panel diagnosis as an additional method to exceed the possibly narrowed perspective of the individual (Chapter 5). The word “additional” in the last sentence is important: we did not replace objective measurement by subjective judgment, we just added expert opinion in order to counterbalance individual preferences, because the interpretation of test results for the domain dizziness in primary care is highly subjective (e.g., if a dizzy patient meets the diagnostic criteria for otitis media it is still uncertain if this diagnosis actually contributes to symptoms of dizziness in this patient).

But where is the control group? In the Annals Journal Club, an online discussion forum for featured articles by the Annals of Family Medicine, Termee et al. responded to the publication of the results of the cross-sectional diagnostic study (Chapter 5) and criticized the lack of a control group. First of all, we actually did perform the diagnostic evaluation among a control group of 115 non-dizzy older persons [Dros/Maarsingh et al., work in progress]. However, although a control group may definitely widen our perspective on dizziness, it is not the solution for the diagnostic dilemmas dizziness confronts us with. Even if
a diagnostic test reveals a statistically significant difference between dizzy patients and controls (e.g., study of Colledge et al., limited neck movement in 52% of dizzy subjects vs. 36% in controls, $P$ value of 0.023), we do not know if the evaluated target condition (in this example neck disease) actually contributes to symptoms of dizziness, because we lack information about the diagnostic accuracy of this test. At this moment, only few diagnostic tests recommended by guidelines on dizziness have been evaluated in a diagnostic accuracy study; none of the recommended tests have been evaluated in an accuracy study performed among patients representative of primary care patients (Chapter 3). Because of this huge lack of empirical evidence, the interpretation of the results of diagnostic tests performed among unselected dizzy primary care patients is delicate business. Panel diagnosis can be an instrument to deal with this diagnostic uncertainty.

And other study designs?
With the present state of the science, there is no study design that will solve the diagnostic dilemmas dizziness confronts us with. However, we strongly believe that a combination of different study designs, especially when applied to the same study population, may widen our perspective. Therefore, the research group DIEP initiated several studies with different designs using data from the same population of 417 older dizzy primary care patients: a cross-sectional diagnostic study using panel diagnosis (Chapter 5), a cross-sectional observational study using principle component analysis (Chapter 6), a cross-sectional prediction study (Chapter 7), a case-control study [Dros/Maarsingh et al., work in progress] with the aim to identify clinically relevant differences between dizzy and non-dizzy persons, and a follow-up study [Dros/Maarsingh et al., work in progress] with the aim to identify predictors of persistent or disabling dizziness in older patients in primary care. All these study designs have their individual limitations, but together they may enable us to expand our perspective on dizziness.

Apples and oranges: the importance of being population-aware
“Heart, Not Ear, Main Source of Dizziness in Elderly”, stated MedPage Today, after the publication of the results of our cross-sectional diagnostic study (Chapter 5). A director of a tertiary care dizziness clinic responded immediately by e-mail and wrote that we heavily had underestimated the contribution of vestibular disease as a cause of dizziness. Perhaps his response was the result of insufficient awareness
of our studied population, as the probability of a condition highly depends on the observed population.\textsuperscript{11} Of course we do not doubt vestibular disease to be the main cause of dizziness in selected tertiary care patients;\textsuperscript{2, 12-17} we just provide additional information about a different - but voluminous – population, showing cardiovascular disease to be the main contributory cause of dizziness among older primary care patients.

As most studies on dizziness - both observational and diagnostic accuracy studies - have been performed among a spectrum of patients not representative of primary care patients, it is difficult to compare the results of the studies described in this thesis with previous research. As a consequence, the interpretation of our results requires a certain “population-awareness”, which is illustrated below.

**Observational studies**

In Chapter 2, we reported a prevalence of dizziness in older patients of less than 10\%, which is much lower than previously reported prevalence rates among older persons (15\%-50\%).\textsuperscript{18-23} However, these studies were carried out in community-based populations and included a spectrum of patients not representative of primary care patients. Probably, many persons experience symptoms of dizziness, but only some visit a physician because of this symptom.

In Chapter 5, we reported cardiovascular disease to be the main contributory cause of dizziness, which seems to conflict with the results of most previous studies. Again, however, this may be due to population differences, varying from younger populations (i.e. lower probability of cardiovascular disease),\textsuperscript{1, 24-28} a vertiginous population (i.e. selection of the dizziness subtype vertigo, with a much higher probability of vestibular disease),\textsuperscript{24} populations seen in emergency departments (i.e. selected patients with acute, worrying dizziness, often of the subtype vertigo),\textsuperscript{25-27} to referred populations (i.e. highly selected population, in the Netherlands less than 5\% of all dizzy patients).\textsuperscript{2, 12-17, 29}

**Diagnostic accuracy studies**

Especially when interpreting diagnostic accuracy studies (Chapter 3) it is important not to neglect population differences, as different populations may have different prevalence rates, and - according to Bayes’ theorem - a change of prevalence of a condition immediately affects the predictive ability of a test used to diagnose this
condition.\textsuperscript{11} We will illustrate this phenomenon by means of a probability calculation\textsuperscript{30} for an imaginary test “X” (target condition: vestibular disease; sensitivity: 90%; specificity: 80%). If we use test X in a dizzy tertiary care population (estimated prevalence of vestibular disease: 30%; Chapter 3), the calculated positive predictive value is 66% (i.e. 66% of the patients with a positive test result are correctly diagnosed; PPV) and the negative predictive value is 95% (i.e. 95% of the patients with a negative test result are correctly diagnosed; NPV).\textsuperscript{11, 30} If we use the same test in a population of older dizzy patients primary care patients (estimated prevalence: 10%)\textsuperscript{31-33} the calculated PPV changes into 33% and the NPV into 99%.\textsuperscript{30} Consequently, a negative result of test X, when applied among older dizzy primary care patients, will provide high certainty about the absence of vestibular disease; a positive test result, however, will provide only little certainty about the presence of vestibular disease. In short, tests with satisfying predictive values in a tertiary care setting may become useless when applied in a primary care setting. A visual representation of Bayes’ theorem for this example is presented in Appendix 1.\textsuperscript{34}

Adding more diagnostic tests: more information or just more data?

After the publication of the results of the cross-sectional diagnostic study (Chapter 5) we received several e-mails with the following comment: “Your research group used diagnostic tests A, B, and C, but you did not use test D. If you would have used test D, the contribution of test-D-related-diagnoses as a cause of dizziness would have been higher.”

Why were diagnostic tests excluded?

As the number of described tests for evaluating dizziness is inexhaustible (mostly observational studies, sometimes diagnostic accuracy studies) and guidelines on dizziness are contradictory,\textsuperscript{35-45} we wanted to separate chaff from wheat. For that reason, we systematically identified and assessed all empirical evidence on diagnostic tests for evaluating dizziness (Chapter 3). In addition, we identified relevant guidelines on dizziness, (pre)syncope, or vertigo. Finally, we combined the collected evidence with expert opinion, in order to select diagnostic tests for our study (Chapter 4, Delphi procedure). During each step, potential diagnostic tests could be excluded. For example, many diagnostic tests were excluded during the systematic review, because they were not feasible for use in general practice (e.g. electronystagmography, specialized imaging techniques, and tilt table testing). In
addition, 15 out of 36 diagnostic tests were excluded during the Delphi procedure, mostly because the panel questioned the technical feasibility of a test (e.g. carotid sinus massage), the diagnostic accuracy of a test (e.g. the head-shaking nystagmus test), or the added diagnostic value of a test (e.g. the Berg Balance Scale).

**Did the exclusion of diagnostic tests affect the results?**

Obviously, more testing means more data. And of course, excluding a diagnostic test always implies the risk of missing essential information. However, we seriously doubt if additional diagnostic data would have improved our ability to discriminate causes of dizziness in our study population.

First of all, we believe that the clinical history is the key diagnostic tool when discriminating causes of dizziness in primary care patients, and that additional diagnostic testing is only of limited value. In a study among 100 consecutive adult outpatients with persistent dizziness, Kroenke et al. reported that 76% of the established causes of dizziness were based on the history alone, while routine physical examination did not often change the diagnosis. Sloane et al. studied 116 consecutive older dizzy patients visiting a neurotology clinic and reported history taking to be the most important diagnostic tool, as the history alone provided the critical diagnostic data in nearly 70% of the patients. The results of the principal component analysis (Chapter 6) also demonstrate the importance of thorough history taking: additional information on physical examination and diagnostic tests (i.e. 30 added variables) did not identify new diagnostic profiles, but only confirmed the diagnostic information provided by history taking alone. Furthermore, almost all diagnostic tests for evaluating dizziness have been studied in selected patients seen in a secondary/tertiary care setting (Chapter 3). As demonstrated previously (Appendix 1), using such tests in unselected primary care patients (i.e. patients with a much lower prevalence of conditions related to dizziness) will lead to a much higher proportion of false positive test results, which negatively affects the overall discriminative ability of our diagnostic evaluation. Finally, it is important to realize that we aimed to discriminate nine groups of causes of dizziness (i.e. adverse drug effect, cardiovascular disease, locomotor disease, endocrine conditions, neurological disease, psychiatric disease, vestibular disease, impaired vision, and other causes), instead of hundreds of specific causes of dizziness. Obviously, the latter would require additional diagnostic testing.
Recommendations for future research

Work in progress

At this moment, there is still work in progress. First, we have performed our standardized diagnostic evaluation (*Chapters 4 en 5*) also among 115 control patients aged 65 years or older without dizziness. Aim of this case-control study is to identify clinically relevant differences between dizzy and non-dizzy older persons in primary care. Second, we have performed a follow-up study among our study population of 417 dizzy patients. Aim of this study is to identify predictors of persistent or disabling dizziness in older patients in primary care. Finally, we have performed a validation study of the Dutch version of the Dizziness Handicap Inventory in a primary care setting, because all questionnaires for dizziness-related disability have been developed and validated in a non-primary care setting.

Loose ends

With the results presented in this thesis, there are some loose ends. First, before implementing the diagnostic dizziness profiles presented in *Chapter 6*, it is necessary to validate the dizziness profiles in another dizzy primary care population. Furthermore, the prediction model presented in *Chapter 7* may lead to a diagnostic decision rule that improves the recognition of anxiety and depression in older dizzy primary care patients. However, necessary steps towards an applicable and useful decision rule include external validation in a new dizzy population, development of a score chart, and investigation of the ability of the decision rule to influence medical decision-making and improve relevant outcomes. Finally, it may be worthwhile to perform a case vignette study in order to assess the generalizability of the diagnoses made by our panel (*Chapter 5*).

New research

As patients with dizziness are managed largely at primary care level, it is not acceptable that none of the recommended diagnostic tests have been validated in primary care patients. Therefore, it is necessary to perform accuracy studies on tests for diagnosing dizziness among a spectrum of patients representative of primary care. As we consider the clinical history to be the key diagnostic tool when evaluating dizziness, it would be worthwhile to assess the diagnostic value of (elements of) history taking for diagnosing conditions related to dizziness. Furthermore, several research groups have suggested that dizziness may be a geriatric syndrome, similar
to delirium and falling. Geriatric syndromes are multifactorial health conditions that occur when the accumulated effect of impairments in multiple systems renders a person vulnerable to situational challenges. According to Olde Rikkert and Schoon, the results of our cross-sectional diagnostic study (Chapter 5) have added evidence to the geriatric syndrome status of dizziness. From this point of view, it would be worthwhile to investigate an impairment reduction strategy for older dizzy patients in general practice (i.e. reducing symptoms and disabilities associated with dizziness, rather than trying to define a single mechanism and unifying diagnosis), for example by means of a multicomponent intervention trial. Finally, as the time of a consultation in daily practice is limited, it is not realistic for general practitioners to aim for an extensive diagnostic evaluation of each dizzy patient. Therefore, it is necessary to perform additional research that focuses on the development of an easy-to-use diagnostic algorithm for causes of dizziness in general practice.

Recommendations for clinical practice
First of all, understanding the clinical epidemiology of dizziness in its corresponding population is an essential first step when evaluating dizziness. Until now, most guidelines on dizziness focus on vestibular disease as the main cause of dizziness. We advocate a change of focus from vestibular to cardiovascular disease when evaluating older dizzy patients in general practice. Second, as most older dizzy patients have more than one cause of dizziness, we recommend a systematic exploration of (categories of) causes of dizziness in order to reveal contributory causes that are amenable to treatment. An approach that considers multiple causes of dizziness may, if not solve the problem of dizziness, lead to a clinically relevant reduction of impairments that contribute to dizziness. Third, as an adverse drug effect was found to be a contributory cause of dizziness in one-quarter of all dizzy patients, we strongly recommend to perform a medication check during the evaluation of older dizzy patients in general practice. Finally, we recommend general practitioners to consider the existence of anxiety and depression in older patients presenting with dizziness, especially because patients with both psychological and physical symptoms tend to have a worse prognosis and effective treatment is available.

In line with the recommendations above it would be worthwhile to create an addendum “dizziness in older patients” to the guideline “Dizziness” of the Dutch College of General Practitioners.
Appendix 1. How a change of prevalence affects the predictive ability of a test: a visual representation of Bayes’ theorem

During the interpretation of diagnostic accuracy studies it is important not to neglect population differences, as different populations may have different prevalence rates, and - according to Bayes’ theorem - a change of prevalence of a condition immediately affects the predictive ability of a test used to diagnose this condition. We will demonstrate the impact of this phenomenon for an imaginary diagnostic test “X” with sensitivity 90% and specificity 80%. The figure above gives a visual representation of Bayes’ theorem [Baggen et al., NTVG 1984]. The horizontal axis in this figure represents the prevalence of a certain target condition (example: vestibular disease) in two different study populations, respectively a population of dizzy patients seen in tertiary care (estimated prevalence of 30%) and a population of older dizzy patients seen in primary care (estimated prevalence of 10%). The left vertical axis represents the specificity of a test, and the right vertical axis represents the sensitivity of a test. The vertical lines at 10% and 30% represent the characteristics of test X, when applied to populations with a prevalence of respectively 10% and 30%; each vertical line is divided into four parts, representing respectively the proportion of true negatives (TN; upper part of vertical line), false negatives (FN; second part of vertical line), false positives (FP; third part of vertical line), and true positives (TP; lower part of vertical line). As the figure clearly demonstrates, a change of prevalence from 30% to 10% will increase the proportion of true negatives (TN/TN+FN; negative predictive value), but it will decrease the proportion of true positives even more (TP/TP+FP; positive predictive value). As a result, a positive result of test X, when applied among older primary care patients, will only provide little certainty about the presence of vestibular disease.
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