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Publication I: participation in the study design, identifying and recruiting participants, data collection, ascertainment of cases, participation in data analysis, writing and revising the manuscript.

Publications II, III: participation in the study design, participation in data collection, ascertainment of cases, participation in data analysis, writing and revising the manuscript.

ABBREVIATIONS

CH	Cluster headache
CDH	Chronic daily headache
ICHD	International Classification of Headache Disorders
MOH	Medication overuse headache
NDPH	New daily persistent headache
TAC	Trigeminal autonomic cephalalgia
TTH	Tension-type headache

1. INTRODUCTION

Primary headaches are headache disorders that do not result from another medical condition but are independent entities with different, although still not completely understood, pathophysiological mechanisms. Primary headaches include migraine, tension-type headache (TTH), trigeminal autonomic cephalalgias (TACs) and a rather heterogeneous group termed other primary headache disorders. These four large categories consist of numerous diverse headache subtypes and distinct diagnostic entities (Headache Classification Committee of the International Headache Society, 2018).

Primary headaches do not only cause considerable personal suffering and loss of quality of life but are a significant public health issue and a source of remarkable societal burden (Steiner *et al*, 2014; Global Burden of Disease, 2015; Messali *et al*, 2016; Saylor and Steiner, 2018). Migraine and TTH are both among the top six most prevalent diseases in the world and migraine is the second leading cause of years lived with disability globally (Vos *et al*, 2017).

Epidemiological studies create the basis for the assessment of disease patterns, burden, cost and need for health services in society (Steiner *et al*, 2013; Stovner *et al*, 2014). The epidemiological data on primary headaches have been steadily growing in the last two decades worldwide (Stovner *et al*, 2007; Stovner and Andree, 2010; World Health Organization and Lifting The Burden, 2011; Saylor and Steiner, 2018). However, in some regions, like in Eastern Europe, gaps are still notable. The prevalence of primary headaches in Estonia has not been studied previously.

Large population-based epidemiological studies are usually resource and time consuming (Stovner *et al*, 2014). In the face of rapid digital evolution it would be beneficial to search for new methods for epidemiological surveys that could exploit the contemporary fast development of information technology. It certainly could be the case in headache epidemiology, bearing in mind that most primary headaches can be diagnosed based on history and do not require additional instrumental investigations (Mitsikostas *et al*, 2017).

Estonia is one of the leading countries in the world regarding the usage of internet and web-based solutions per household (International Telecommunication Union, 2017). In 2019 Estonia ranked 8th out of the 28 European Union Member States in the European Commission Digital Economy and Society Index, a composite index that summarises relevant indicators on member states' digital performance, showing that the use of internet services remains consistently high in this country (European Commission, 2019). The digital economy and society index comprises, among other aspects, connectivity, human digital inclusion and skills, use of internet services, integration of digital technology and digital public services. The aforementioned aspects set up potentially promising conditions for using e-technology in performing representative studies in headache epidemiology in Estonia.

2. REVIEW OF THE LITERATURE

2.1 Classification of primary headaches

Today headache is one of the most thoroughly classified neurological diseases. The first edition of International Classification of Headache Disorders (ICHD) was published in 1988. It was primarily based on the opinions of experts and the main purpose of it was to establish operational diagnostic criteria for different headache disorders to enable and increase nosographic and epidemiologic research. The authors readily admitted, and in fact it was one of its goals, that extensive studies must be conducted to make the classification more evidence-based (Headache Classification Committee of the International Headache Society, 1988). The first edition of ICHD was followed by the second in 2004 and it included changes prompted by new evidence and revised opinions of experts (Headache Classification Subcommittee of the International Headache Society, 2004). The latest ICHD third edition (Headache Classification Committee of the International Headache Society, 2018) was preceded by a beta version in 2013 (Headache Classification Committee of the International Headache Society, 2013). The idea behind this beta version was to allow more field testing before publication of the final ICHD-3 in 2018, and as the authors concluded, had worked well since new scientific evidence played a significantly increasing role in the changes made in ICHD-3.

Both the ICHD-3 beta and ICHD-3 consist of three parts – the primary headaches, the secondary headaches and thirdly painful cranial neuropathies, other facial pains and other headaches.

The first part, primary headaches, consists of four major entities: migraine, tension-type headache, TACs and other primary headache disorders. These disorders are further subclassified hierarchically, giving the possibility to make a headache diagnosis with relevant degree of detail, ranging from the general first-digit level to the most detailed fifth-digit level diagnosis.

In epidemiological studies the diagnoses are usually made with second-digit accuracy, with some specific deliberations related to the nature of epidemiological research (Stovner *et al*, 2014). The ICHD second-digit level diagnoses for migraine and TTH that are important from the epidemiological research perspective are migraine with or without aura, chronic migraine, probable migraine, frequent episodic tension-type headache, chronic tension-type headache and probable tension-type headache. TACs and other primary headache disorders are rare entities with numerous subdivisions. The TACs' second-digit level diagnoses include cluster headache (CH), paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks, hemicrania continua and probable TACs. The other primary headache disorders include the following ten second-digit level diagnoses: primary cough headache, primary exercise headache, primary headache associated with sexual activity, primary thunderclap headache, cold-stimulus headache, external-pressure headache, primary stabbing headache,

nummular headache, hypnic headache and new daily persistent headache (NDPH) (Headache Classification Committee of the International Headache Society, 2013 and 2018).

2.2 Methodology of population surveys of headache prevalence

For the last two decades the recognition of the magnitude of the impact of headaches on personal as well as societal level has been steadily growing (Steiner *et al*, 2014; Global Burden of Disease, 2015; Messali *et al*, 2016; Saylor and Steiner, 2018). This has largely stemmed from the increasing evidence on headache epidemiology. However, several reviews of the world literature on the topic (Stovner *et al*, 2006; Stovner *et al*, 2007, Stovner and Andree, 2010) showed significant variations and a number of shortcomings in the methodology of headache epidemiology studies and the need for standardized approach became evident (Steiner *et al*, 2013). Lifting The Burden, a United Kingdom non-profit organization in official relations with World Health Organization (Steiner *et al*, 2011) with the priority to fill the knowledge gaps of headache epidemiology and burden (Saylor and Steiner, 2018), engaged an expert panel to develop consensus guidelines on the principles of conduct of cross-sectional population-based studies of headache. The guidelines were published in 2014 (Stovner *et al*, 2014) and the detailed document includes recommendations with extensive explanatory commentary on ethical issues, study design, population of interest, control of bias, sample selection and avoidance of selection bias, accessing and engaging participants, participation rate and non-participation, method of enquiry, case definition and diagnosis, aspects of pilot study, data collection and storage and reporting the study. In addition, the authors proposed criteria and a scoring system for evaluating the quality of headache prevalence studies. Very shortly and in general, a headache prevalence study of good quality should be conducted on general population or community-based sample from defined region within a country, has a random sample corrected for population demographics, has a number of respondents >1500, has a participation rate of >70%, accesses the participants by telephone or face-to-face interview by trained interviewers, has a validated diagnostic instrument with sensitivity and specificity >70%, uses ICHD diagnostic criteria and has a prevalence time frame of specified period appropriate to the study purpose (mostly point, one-year or lifetime prevalence) (Stovner *et al*, 2014).

2.2.1 Headache diagnoses in headache epidemiology research

In all epidemiologic studies, it is of fundamental importance to define caseness, in other words who has a certain diagnosis and who has not (Stovner *et al*, 2006; Stovner *et al*, 2014). The aforementioned consensus guidelines of population

surveys of headache prevalence (Stovner *et al*, 2014) stipulate that all the studies should use the most recent ICHD criteria for determining headache cases. However, the authors agree that since the ICHD criteria were not designed for epidemiological studies, several justified deliberations are inevitable. For example, it is recommended not to distinguish between migraine with and without aura, because it is nearly impossible to diagnose aura by a questionnaire (Stovner *et al*, 2007; Stovner and Andree, 2010, Stovner *et al*, 2014). When speaking about headache occurring on ≥15 days per month, it is acceptable not to differentiate further if it is a chronic TTH, chronic migraine or any other type of chronic headache, since it is recognized that precise diagnosis is difficult at an one-time encounter with the study subject (Stovner *et al*, 2014). The synonymously used terms „headache on ≥15 days per month", „chronic headache" or „chronic daily headache" are not independent entities defined in ICHD (Headache Classification Committee of the International Headache Society, 1988, 2004, 2013 and 2018), however, these terms refer to a subset of headache disorders that are most incapacitating, have a severe socioeconomical impact and thus are an important issue in headache epidemiology research (Stovner *et al*, 2007; Stovner and Andree, 2010; Steiner *et al*, 2013; Stovner *et al*, 2014; Global Burden of Disease, 2015; Messali *et al*, 2016). Many epidemiological studies also incorporate medication overuse headache (MOH) for the same reason (Stovner and Andree, 2010; Stovner *et al*, 2014, Saylor and Steiner, 2018), although MOH is not a primary headache, but a secondary one developing as a consequence of regular overuse of acute headache medication (Headache Classification Committee of the International Headache Society, 2004, 2013 and 2018; Vandenbussche *et al*, 2018). Large population-based surveys usually do not study other secondary headaches because reasonably certain diagnosis of a secondary headache requires extensive clinical and medical investigations, and often follow-up, which is not feasible in most population-based epidemiologic studies (Stovner and Andree, 2010).

2.2.2 Timeframe of headache in headache epidemiology research

The most widely used timeframe in headache epidemiology research has been one-year prevalence (Stovner *et al*, 2007; Stovner and Andree, 2010, Steiner *et al*, 2013; Stovner *et al*, 2014) and therefore allows the most comparisons with other studies. This corresponds to the term „active headache disorder" defined in ICHD-2 and characterized by any occurrence of headache during the last year (Headache Classification Committee of the International Headache Society, 2004; Stovner *et al*, 2014). However, this timeframe is not free from recall bias and thus very short and recent timeframes have been applied – 1-day prevalence, or „headache today/yesterday" (Yu *et al*, 2013; Andree *et al*, 2014; Stovner *et al*, 2014; Ayzenberg *et al*, 2015, Steiner *et al*, 2016). These avoid recall bias almost entirely, but do not describe the whole proportion of population with an active headache disorder as one-year prevalence does (Stovner *et al*, 2014). The longest

timeframe, lifetime prevalence, has also been quite widely implemented (Stovner *et al*, 2007; Stovner and Andree, 2010), but is expectedly most vulnerable to recall bias. Lifetime prevalence is of most interest in rare headache disorders and also in genetic epidemiological studies, in the latter to eliminate those who have ever had the disorder from control groups (Stovner *et al*, 2014).

2.3 Prevalence of headache in general

2.3.1 Europe

A review article on the prevalence of headache in Europe published in 2010 (Stovner *et al*, 2010) found the one-year prevalence of all headache among adults in Europe to be 53%, ranging from 29% in Greece (Mitsikostas *et al*, 1996) to 76% in United Kingdom (Boardman *et al*, 2005), and the lifetime prevalence of headache in Europe to be 77%, ranging from 35% in France (Henry *et al*, 1992) to 96% in Denmark (Rasmussen *et al*, 1991). The review covered 49 studies, among which 21 studies on adult populations from different European countries presented one-year and lifetime prevalences on headache in general (Waters *et al*, 1975; Crisp *et al*, 1977; Nikiforow *et al*, 1981; D'Alessandro *et al*, 1988; Rasmussen *et al*, 1991; Henry *et al*, 1992; Gobel *et al*, 1994; Laínez *et al*, 1994; Pereira Monteiro *et al*, 1995; Mitsikostas *et al*, 1996; Hagen *et al*, 2000; Dahlof and Linde, 2001; Zivadinov *et al*, 2001 and 2003; Boardman *et al*, 2003 and 2005; Lampl *et al*, 2003; Boru *et al*, 2005; Russell *et al*, 2008; Katsarava *et al*, 2009; Radke *et al*, 2009). The authors explained the large variations in prevalence estimates by methodological differences between studies. Another study conducted in Italy and published in 2009 but not included in the previous review, found a lifetime prevalence of all primary headaches combined at 52% (Schwaiger *et al*, 2009).

A cross-sectional study conducted by the Eurolight Project of 8271 participants from selected European countries (Austria, France, Germany, Italy, Lithuania, Luxembourg, the Netherlands, Spain and the United Kingdom) published in 2014 reported an even higher gender-adjusted one-year prevalence of all headaches at 78.6% and a lifetime prevalence of 91.3% (Steiner *et al*, 2014).

Later studies conducted by Lifting The Burden with standardized methodology (Steiner *et al*, 2014) in Eastern-European countries, namely Georgia (Katsarava *et al*, 2009), Lithuania (Rastenytė *et al*, 2017), Moldova (Moldovanu *et al*, 2007) and Russia (Ayzenberg *et al*, 2012), reported an one-year prevalence of all headache in the somewhat narrower range of 54–75% (Saylor and Steiner, 2018).

2.3.2 Other regions

Stovner *et al* estimated the mean prevalence of headache in general to be close to 50% in all other regions of the world except for Africa, where it was about 20%, in a review article published in 2007 (Stovner *et al*, 2007). This review included studies from all over the world and the one-year prevalences found in different countries from different regions other than Europe were ranging as follows: Africa 20–23% (Levy, 1983; Dent *et al*, 2004), Asia 29–79% (Sakai and Igarashi, 1997; Roh *et al*, 1998; Wang *et al*, 2000; Deleu *et al*, 2002; Takeshima *et al*, 2004), Australia/Oceania 50% (Paulin *et al*, 1985), North America 13–87% (O'Brien *et al*, 1994; Kryst and Scherl, 1994; Schwartz *et al*, 1997) and Central and South America 29–63% (Jaillard *et al*, 1997; Wiehe *et al*, 2002; Miranda *et al*, 2003). Again, large variations are evident and the same applies for the lifetime prevalences from the studies from the countries from different regions: Africa 51% (Osuntokun *et al*, 1992), Asia 8–82% (Abduljabbar *et al*, 1996; Alders *et al*, 1996; Sakai and Igarashi, 1997; Ho and Ong, 2003), North America 16–87% (Ziegler et al, 1977; Duckro et al, 1989; Kryst and Scherl, 1994; O'Brien *et al*, 1994; Carson *et al*; 2004) and Central/South America 73–94% (Wiehe *et al*, 2002; Benseñor *et al*, 2003). No studies were found from Australia/Oceania reporting lifetime prevalences.

Since 2007, several other papers have been published, including studies conducted by Lifting The Burden (Saylor and Steiner, 2018). These studies have intentionally covered various world regions and have revealed more uniform one-year prevalences of all headache except for the low 24% in China (Yu *et al*, 2012). The studies report one-year prevalences from India (Kulkarni *et al*, 2015), Nepal (Manandhar *et al*, 2015), Pakistan (Herekar *et al*, 2017), Ethiopia (Zebenigus *et al*, 2017), Zambia (Mbewe *et al*, 2015) and Saudi Arabia (Al Jumah *et al*, 2020) that range from 45–85%. It has been concluded that since the methodology of these studies is similar, the differences are due to other geographical, socio-economic or genetic factors (Saylor and Steiner, 2018).

2.4 Prevalence of migraine

The literature on migraine prevalence is no doubt the most abundant among other primary headaches and the prevalence rates are more consistent compared to other headache disorders. Migraine is also famous for its gender difference – it is known to be two to three times more prevalent in women than in men (Stewart *et al*, 1992; Russell *et al*, 1995; Steiner *et al*, 2003; Stewart *et al*, 2008; Buse *et al*, 2013).

2.4.1 Europe

Stovner *et al* reported a 15% (18% in females, 8% in males) mean one-year and a 16% (20% in females, 11% in males) lifetime prevalence of episodic migraine among 170,000 adults in Europe in their review article from 2010 (Stovner *et al*, 2010). The calculations were based on 31 studies from different European countries that reported one-year prevalences ranging from 10% to 25% and lifetime prevalences from 9% to 28% (Rasmussen *et al*, 1991; Henry *et al*, 1992 and 2002; Gobel *et al*, 1994; Laínez *et al*, 1994; Merikangas *et al*, 1994; Pereira Monteiro *et al*, 1995; Russell *et al*, 1995 and 2006; Michel *et al*, 1996; Launer *et al*, 1999; Bank *et al*, 2000; Hagen *et al*, 2000; Mattsson *et al*, 2000; Dahlöf and Linde, 2001; Zivadinov *et al*, 2001 and 2003; Kececi *et al*, 2002; Lampl *et al*, 2003; Steiner *et al*, 2003; Boru *et al*, 2005; Celik *et al*, 2005; Lanteri-Minet *et al*, 2005; Lyngberg *et al*, 2005; Molarius *et al*, 2006; Russell *et al*, 2008; Sjaastad and Bakketeig, 2008; Katsarava *et al*, 2009; Pfaffenrath *et al*, 2009; Radke *et al*, 2009). The Bruneck Study from Italy published in 2009 found somewhat lower one-year and lifetime prevalence rates of migraine at 6% (8% in females, 3% in males) and 19% (29% in females, 9% in males), respectively (Schwaiger *et al*, 2009).

The later cross-sectional study by the Eurolight Project from selected European countries reported a higher 35% one-year prevalence of migraine (43% in female, 26% in male) (Steiner *et al*, 2014). However, studies conducted by Lifting The Burden (Steiner *et al*, 2014) in Eastern-European countries reveal results that are more in concordance with the aforementioned earlier studies from Europe, namely one-year migraine prevalences ranging from 16% in Georgia to 20% in Russia (Moldovanu *et al*, 2007; Katsarava *et al*, 2009; Ayzenberg *et al*, 2012; Rastenytė *et al*, 2017; Saylor and Steiner, 2018).

2.4.2 Other regions

In the review article by Stovner *et al* from 2007 it is estimated that outside Europe current migraine is most prevalent in the Americas (around 9–14%) and least prevalent in Africa (5%) (Stovner *et al*, 2007). The one-year prevalences of migraine found in countries from different regions other than Europe were ranging as follows: Africa 3–5% (Tekle Haimanot *et al*, 1995; Dent *et al*, 2004), Asia 6–22% (Alders *et al*, 1996; Sakai and Igarashi, 1997; Roh *et al*, 1998; Wang *et al*, 2000; Deleu et al, 2002; Takeshima *et al*, 2004), North America 9–15% (Stewart *et al*, 1992 and 1996; Kryst and Scherl, 1994; O'Brien *et al*, 1994; Schwartz *et al*, 1997; Lipton *et al*, 2001 and 2002; Patel *et al*, 2004) and Central and South America 5–14% (Jaillard *et al*, 1997; Lavados and Tenhamm, 1997; Miranda *et al*, 2003; Morillo *et al*, 2005). The more scarcely reported lifetime prevalences of migraine in countries from different regions were: Africa 5% (Osuntokun *et al*, 1992), Asia 3.1% (Ho *et al*, 2003), North America 8–17% (O'Brien *et al*, 1994; Carson *et al*; 2004) and Central and South America 16%

(Wiehe *et al*, 2002). No studies on migraine prevalence were found from Australia/Oceania (Stovner *et al*, 2007).

American Migraine Prevalence and Prevention Study, a large-scale population-based migraine prevalence study with a sample of more than 160 000 individuals from United States conducted in 2004 but not included in the aforementioned review, found the one-year prevalence of all migraine to be 16% (females 22.6%, males 9.6%) (Lipton *et al*, 2007; Buse *et al*, 2013).

The later studies by Lifting The Burden initiative have revealed one-year prevalences from China at 9% (Yu *et al*, 2012), India at 25% (Kulkarni *et al*, 2015), Nepal at 35% (Manandhar *et al*, 2015), Pakistan at 22% (Herekar *et al*, 2017), Ethiopia at 18% (Zebenigus *et al*, 2017), Zambia at 23% (Mbewe *et al*, 2015) and Saudi Arabia at 25% (Al Jumah *et al*, 2020).

A comprehensive review of migraine epidemiology and burden in East Asia published in 2019 reported an one-year migraine prevalence of 6–14% in the region (Takeshima *et al*, 2019). The study included 11 population-based studies in adults in China, Japan and South-Korea, four of which reported one-year prevalences (Takeshima *et al*, 2004; Kim *et al*; 2012; Yu *et al*, 2012; Luo *et al*, 2014).

2.5 Prevalence of TTH

On one hand, TTH has generally been known to be the most prevalent primary headache disorder (Stovner *et al*, 2007; Steiner *et al*, 2014; Saylor and Steiner, 2018). On the other, studies conducted and published on the prevalence of TTH are much more scarce when compared to the relative multitude of studies on migraine. Furthermore, different prevalence studies on TTH have revealed notoriously variable results (Stovner *et al*, 2007; Stovner and Andree, 2010). Possible reasons for this diversity have been suspected to lie in the differences in the methodological approaches across studies, diagnostic overlap of TTH with probable migraine, differences in headache awareness, socioeconomic, genetic or environmental factors (Sahler, 2012; Steiner *et al*, 2013; Stovner *et al*, 2014).

2.5.1 Europe

Stovner *et al* reported a mean one-year prevalence of TTH in Europe of 63% among more than 66 000 adults, an estimation based on nine studies in their review paper from 2010 (Stovner *et al*, 2010). The analysis included studies from Croatia (Zivadinov *et al*, 2003), Denmark (Rasmussen *et al*, 1991; Lyngberg *et al*, 2005; Russell *et al,* 2006), Georgia (Katsarava *et al*, 2009), Germany (Gobel *et al*, 1994; Radtke *et al*, 2002; Pfaffenrath *et al*, 2009), Portugal (Pereira Monteiro, 1995) and Turkey (Koseoglu *et al*, 2003) and the one-year and lifetime prevalences ranged from 19–86% and 35–78%, respectively.

The later cross-sectional study by the Eurolight Project from selected European countries reported a lower 38% one-year prevalence of TTH (Steiner *et al*, 2014) as compared to the previous review. So do the studies conducted by Lifting The Burden (Steiner *et al*, 2014) in Eastern-European countries: they reveal one-year prevalences of TTH ranging from 31–42% in Russia, Georgia and Lithuania (Katsarava *et al*, 2009; Ayzenberg *et al*, 2012; Rastenytė *et al*, 2017; Saylor and Steiner, 2018) and an exceptionally low 18% in Moldova (Moldovanu *et al*, 2007).

2.5.2 Other regions

In the review article by Stovner *et al* from 2007 it was estimated that the global one-year prevalence of TTH is 42% and the lifetime prevalence of TTH is 46% (Stovner *et al*, 2007). These rates were based on a small number of studies from around the world, whereas none could be found from Africa, Australia and Oceania. Three studies form Asia reported one-year prevalences ranging from 22–27% (Alders *et al*, 1996; Takeshima *et al*, 2004) and a controversial lifetime prevalence of 13% in Singapore (Ho and Ong, 2003), two studies from North America reported one-year prevalences of 20% (Pryse-Phillips *et al*, 1992) and 40% (Schwartz *et al*, 1998) and two studies from South America reported an one-year prevalence of 27% (Lavados and Tenhamm, 1998) and a lifetime prevalence of TTH of 66% (Wiehe *et al*, 2002).

Studies by Lifting The Burden initiative have revealed one-year prevalences of TTH from China at 11% (Yu *et al*, 2012), India at 35% (Kulkarni *et al*, 2015), Nepal at 41% (Manandhar *et al*, 2015), Pakistan at 45% (Herekar *et al*, 2017), Ethiopia at 21% (Zebenigus *et al*, 2017), Zambia at 23% (Mbewe *et al*, 2015) and Saudi Arabia at 34% (Al Jumah *et al*, 2020).

2.6 Prevalence of chronic headache

Chronic headache or chronic daily headache, although not an independent diagnostic entity, includes different disorders that cause headaches on ≥15 days per month. Chronic headache has a significant impact on affected individuals personally as well as communities socioeconomically and thus is an important topic in headache epidemiology (Stovner *et al*, 2007; Stovner and Andree, 2010; Steiner *et al*, 2013; Stovner *et al*, 2014; Global Burden of Disease, 2015; Messali *et al*, 2016).

Stovner *et al* reported a global mean one-year prevalence of chronic daily headache of 3.4% (Stovner *et al*, 2007). The estimate was based on eleven studies, five from Europe (Rasmussen *et al*, 1991; Mitsikostas *et al*, 1996; Castillo *et al*, 1999; Hagen *et al*, 2000; Henry *et al*, 2002) and six from other regions (Tekle Haimanot *et al*, 1995; Lavados and Tenhamm, 1998; Schwartz *et al*, 1998; Lu *et al*, 2001; Wiehe *et al*, 2002; Takeshima *et al*, 2004) and the individual one-

year prevalence rates of chronic headache ranged from 1.7% in Ethiopia (Tekle Haimanot *et al*, 1995) to 7.3% in Brazil (Wiehe *et al*, 2002). Scher *et al* reported an overall prevalence of chronic headache of 4% in a large population-based study in the United States (Scher *et al*, 1998). A later review from 2010 by Stovner and Andree reported a mean one-year prevalence of chronic daily headache in Europe of 4.0% and this review included three later studies (Wiendels *et al*, 2006; Grande *et al*, 2008; Katsarava *et al*, 2009) in addition to the five previously mentioned ones (Rasmussen *et al*, 1991; Mitsikostas *et al*, 1996; Castillo *et al*, 1999; Hagen *et al*, 2000; Henry *et al*, 2002). The cross-sectional study by the Eurolight Project from nine different European countries published in 2014 reported an almost two times higher 7.6% one-year prevalence of chronic daily headache (Steiner *et al*, 2014).

The cross-sectional studies of Lifting The Burden initiative report varying one-year prevalence rates of headaches on ≥15 days per month (Saylor and Steiner, 2018), ranging from 1% in China (Yu *et al*, 2012) to 12% in Zambia (Mbewe *et al*, 2015). However, these seem to be consistently higher in the Eastern European region, where the results range from 5% in Moldova (Moldovanu *et al*, 2007) to 8% in Georgia (Katsarava *et al*, 2009), 9% in Lithuania (Rastenytė *et al*, 2017) and 10% in Russia (Ayzenberg *et al*, 2012). This tendency has not been explained, although headache on ≥ 15 days per month seems to be especially problematic in the former Union of Soviet Socialist Republics (Saylor and Steiner, 2018).

2.7 Prevalence of TACs

2.7.1 Cluster headache

CH is the most frequent TAC. A meta-analysis published in 2008 revealed a worldwide lifetime prevalence of CH of 0.12% and one-year prevalence of 0.05% (Fischera *et al*, 2008). It included 16 studies: eleven from Europe (Ekbom *et al*, 1978; d'Alessandro et al, 1986; Rasmussen *et al*, 1991; Mitsikostas *et al*, 1994; Pereira Monteiro *et al*, 1999; Tonon *et al*, 2002; Sjaastad *et al*, 2003; Torelli *et al*, 2005; Ekbom *et al*, 2006; Evers *et al*, 2007; Katsarava *et al*, 2007), three from North-America (Swanson *et al*, 1994; Black *et al*, 2005), one from Ethiopia (Tekle Haimanot *et al*, 1995) and one from Malaysia (Alders *et al*, 1996).

A later door-to-door survey in Georgia found the one-year prevalence of CH to be 0,09% (Katzarava *et al*, 2009) and a study on an urban population in Brazil reported a lifetime prevalence of CH of 0.04% (Jurno *et al*, 2018). Steinberg *et al* studied ten-year prevalence of CH among working-aged people in Sweden and estimated it to be 0.05% (Steinberg *et al*, 2019).

2.7.2 Other TACs

Since paroxysmal hemicrania, hemicrania continua and short-lasting unilateral neuralgiform headache attacks are very rare, there is a lack of epidemiological studies addressing the prevalence of these disorders in general population.

Sjaastad *et al* reported finding one individual with probable paroxysmal hemicrania, two individuals with short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (a subform of short-lasting unilateral neuralgiform headache attacks), and one individual with hemicrania continua in a sample of 1838 subjects of 18–65 years in the Vågå study of headache epidemiology in Norway (Sjaastad and Bakketeig, 2007).

2.8 Prevalence of other primary headaches

The epidemiological data on other primary headaches is even scarcer and the findings are somewhat controversial, especially for primary exercise headache and primary stabbing headache.

The Bruneck Study was a prospective population-based study of the epidemiology of cardiovascular and neurological diseases in Italy and one of its goals was to evaluate the prevalence of all primary headaches in the population, including other primary headaches (Schwaiger *et al*, 2008). The authors reported the following one-year and lifetime prevalences, respectively – 1.7% and 2.8% for all other primary headaches combined, 1.2% and 1.2% for primary stabbing headache, 0.2% and 0.2% for primary cough headache, 0.5% and 0.2% for primary exercise headache, 0.5% and 0.2% for hypnic headache and 0.3% and <0.2% for primary thunderclap headache. They did not find any cases of primary headache associated with sexual activity nor of NDPH. Since cold-stimulus headache, external-pressure headache and nummular headache were classified as other primary headaches only in the later published ICHD-3 beta, these entities were not evaluated.

An earlier cross-sectional study of 25–64-year-old general population conducted in Denmark found the lifetime prevalence of primary stabbing headache to be 2%, of external pressure headache 4%, cold stimulus headache 15% and primary cough headache, primary exercise headache and headache associated with sexual activity each of 1% (Rasmussen and Olesen, 1992).

Sjaastad and Bakketeig found the lifetime prevalence of primary exercise headache to be of a rather different magnitude in the Vågå study, namely 12.3% (Sjaastad and Bakketeig, 2002). Rabiee *et al* reported the one-year prevalence of primary exercise headache to be 7.3% in a cross-sectional study in Iran (Rabiee *et al*, 2015). Studies conducted on more specific samples of conscripts and cyclists have revealed even higher prevalence rates of up to 26% (van der Ende-Kastelijn *et al*, 2012; Tofangchiha *et al*, 2016).

The results from the prevalence studies on primary stabbing headache have also been contradictory – the Vågå study of headache epidemiology in Norway

reported the lifetime prevalence of primary stabbing headache at 35.2% (Sjaastad *et al*, 2001) as opposed to the aforementioned significantly lower prevalence rates. It has been proposed that the reason for this discrepancy in case of primary stabbing headache and primary exercise headache is the fact that both of these disorders are known to co-exist with other more bothersome headaches like migraine or CH (Drummond and Lance, 1984; Silbert *et al*, 1991; Pascual *et al*, 2008; Hanashiro *et al*, 2015) and therefore are often left unnoticed (Sjaastad *et al*, 2001; Bahra, 2012).

There are no population-based studies of the prevalence of nummular headache available. More than 250 cases have been reported in the literature (Schwartz *et al*, 2013).

The one-year prevalence of NDPH in general population has been reported to be 0.03–0.1% (Castillo *et al*, 1999; Grande *et al*, 2009).

2.9 Web-based solutions in headache research

Online approaches in headache-related studies have started to appear in the literature during the last decade. Most often these are studies looking into headache symptoms, associated factors, treatment practices or burden.

The web-based studies in migraine research are the most numerous. In 2016 Messali *et al* published a study of direct and indirect costs of episodic and chronic migraine in the United States, where a web-based questionnaire was used to elicit data on topics related to the burden of migraine. The potential study participants were identified by a healthcare company from an online pool of registered panelists and they were screened using web-based tools to find individuals with migraine to be enrolled in the study (Messali *et al*, 2016). An analogous study using online approach called International Burden of Migraine Study had been conducted a few years earlier (Blumenfeld *et al*, 2011). The Migraine in America Symptoms and Treatment Study was a large longitudinal, internet-based panel study of migraine among adults in the United States. The respondents of this study were recruited from a nationwide online research panel and they were screened for migraine by a validated migraine questionnaire (Lipton *et al*, 2018). The study enabled to gather data and draw conclusions on gender differences and treatment patterns (Lipton *et al*, 2018) as well as symptoms (Dodick *et al*, 2019; Munjal *et al*, 2020), associated risk factors and comorbidities (Buse *et al*, 2020), acute medication overuse (Schwedt *et al*, 2018) and unmet acute treatment needs in migraine (Lipton *et al*, 2019). My Migraine Voice survey was a large global study of disease burden among individuals with migraine for whom preventive treatments had failed. The participants were recruited by means of existing online panels and support organizations for people with migraine (Martelletti *et al*, 2018). Several other studies gathering data on migraine symptoms and associated conditions have used online survey design and the participants have been recruited through social media (Wachholtz *et al*, 2017; Hayne and Martin, 2019;

Gelfand *et al*, 2019), web apps (Drescher *et al*, 2019; Farris *et al*, 2019), migraine-related websites (Lee *et al*, 2016) or specialized healthcare centers (Fragoso *et al*, 2019).

CH seems to be the second most frequent headache type that is researched using web-based solutions. Wilbrink *et al* have validated two stepwise web-based questionnaires (LUCA and QATCH) for diagnosing CH for carrying out large-scale epidemiologic and genetic studies in Holland, and showed that such an approach would be accurate and reliable, despite the relatively low sensitivity values of 53.8–57.2% (Wilbrink *et al*, 2013). The same questionnaire was later used in an also web-based study of CH and depression (Louter *et al*, 2016). Di Lorenzo *et al* published results from an online survey of the use of illicit drugs as self-medication among CH patients in Italy. The participants were recruited from a web-based self-help group of CH patients (Di Lorenzo *et al*, 2016). Another online CH survey has also used recruiting participants from cluster headache websites (Schindler *et al*, 2018). Interictal burden of CH was assessed in the Eurolight Cluster Headache Project, an internet-based cross-sectional study of people with CH (Pohl *et al*, 2020).

There are a few studies looking into other headaches besides migraine and CH. A web-based survey of exercise-related headache has been described by van der Ende-Kastelijn *et al* in 2012, where all the participants in a tough cycling event in Holland were invited to fill in an online questionnaire in order to establish the prevalence of primary exercise headache among an athletic population (van der Ende-Kastelijn *et al*, 2012). Bui *et al* studied the incidence of airplane headache and its potential risk factors among Scandinavian air-travellers using an online survey that was distributed through the Facebook-pages of Airlines and interest organisations (Bui *et al*, 2016).

Web-based surveys have been conducted to obtain information about different headache treatment practices and patterns among medical professionals (Dobb and Cooper, 2013; Tassorelli *et al*, 2017; Cowan *et al*, 2019; Dave *et al*, 2019; Dale *et al*, 2020).

2.10 Summary of the literature review

Primary headaches are a thoroughly classified and a rather meticulously described set of disorders in neurology (Headache Classification Committee of the International Headache Society, 1988, 2004, 2013 and 2018). The clear-cut diagnostic criteria for different entities create a reasonable basis for distinguishing separate diagnoses, in spite of sometimes being too mechanistic in clinical practice or epidemiological studies (Stovner *et al*, 2014). The methodology used in the earlier epidemiological research in primary headaches has been rather varied (Steiner *et al*, 2013) but since consensus guidelines on the principles of conduct of cross-sectional population-based studies of headache were published in 2014 (Stovner *et al*, 2014), a shift towards a more standardized approach is evident. The epidemiological data on primary headaches are growing steadily worldwide.

In some regions, like Europe and North-America, multiple studies have been conducted, sometimes repeatedly in the same country, whereas in others, like Africa, South-America and Australia, the data are still largely missing. However, this information is crucial for the assessment of the disease burden and cost and for decision-making in public health in the society. The prevalence of primary headaches in Estonia has also not been studied before. The present study was designed to evaluate the prevalence of primary headaches in Estonia in order to gain data for further health policy planning.

The fast digital evolution, like in almost all other aspects of life, has also been observable in the field of headache and headache epidemiology. Online approaches in headache studies have started to appear since the 2010s, most often looking into headache symptoms, associated factors, treatment practices or burden. Migraine is the most frequent primary headache studied via internet, followed by CH, and a few web-based surveys have been conducted on other primary headaches. However, large internet-based epidemiological studies that encompass all primary headaches and involve a population of a whole country have not been published before. Since traditional large population-based person-to-person epidemiological studies are resource and time consuming, web-based research could be a viable option in technologically highly developed countries. Estonia certainly qualifies as one, being one of the leading countries in the world regarding the usage of internet and web-based solutions per household (International Telecommunication Union, 2017) and ranking high in the European Commission Digital Economy and Society Index (European Commission, 2019). To experimentally and evidentially address the question if web-based approach to the epidemiological studies of primary headache disorders could be useful and applicable, and what pitfalls there might be expected, an online headache questionnaire was developed and tested and a web-based survey on the prevalence of primary headaches was conducted. The results of the web-based survey were compared to the previously mentioned person-to-person population-based epidemiological study in Estonia to assess the differences and biases.

3. AIMS OF THE STUDY

1. To develop and test a questionnaire for headache epidemiological research in Estonia (Paper I)
2. To determine the one-year prevalence of primary headaches among 20–64-year-old population in Estonia (Paper II)
3. To evaluate the applicability of web-based solutions in the epidemiological studies of primary headaches by comparing the results of a web-based survey to the population-based epidemiological study in Estonia (Paper III)

4. PARTICIPANTS AND METHODS

This study was approved by the Research Ethics Committee of the University of Tartu (permissions no. 242T-11 and no. 252T-15). All the participants were informed of the purpose of the study and gave their written or digital informed consent for participation.

4.1 Diagnostic questionnaire for headache epidemiological research in Estonia

4.1.1 Questionnaire

A headache questionnaire was composed in Estonian and named PRILEVEL (acronym from Estonian *PRImaarsete peavalude LEVimus ja ELukvaliteet*, "the prevalence and quality of life with primary headaches") (Appendix A). It consisted of two parts. The first was designed to gather demographic data (age, weight, height, education, habitat (rural or urban)) and the possible headache risk-factors (physical activity, smoking, and coffee and alcohol consumption) of participants. The first part ended with the screening question about the presence of headaches: "During the last year have you had repeated headaches not caused by an acute infection, a medication's side effects, medical procedures, or consumption of toxic substances including alcohol?" If the participant responded affirmatively, (s)he was introduced to the second, diagnostic part of the questionnaire. This was compiled of fourteen questions about different characteristics of headache (localisation, laterality, intensity, character, preceding/accompanying symptoms, frequency, duration, response to indomethacin, association with particular situations/activities, precipitating factors, drug consumption, and history of head trauma). A specifically designed digital algorithm provided a headache diagnosis based on the responses to the questions when possible. The algorithm strictly used the ICHD-3 beta criteria (Headache Classification Committee of the International Headache Society, 2013) to identify the following entities: episodic migraine with or without aura, chronic migraine, TTH (episodic or chronic), CH (episodic or chronic), paroxysmal hemicranias (episodic or chronic), short-lasting unilateral neuralgiform headache attacks (episodic or chronic), primary cough headache, primary headache associated with sexual activity, primary exercise headache, primary stabbing headache, cold-stimulus headache, nummular headache, hypnic headache, NDPH, headache attributed to trauma, trigeminal neuralgia or neuropathy, and MOH. The algorithm always applied the ICHD-3 beta definite criteria for the diagnoses except for two aspects when diagnosing migraine. Firstly, the duration of an attack was allowed to last from four hours to seven days in order to not exclude participants who had attacks typical of migraine but who also had had status migrainosus. Secondly, the definite diagnostic criteria for migraine require the presence of at least one of the following – either nausea or vomiting

or photophobia and phonophobia (Headache Classification Committee of the International Headache Society, 2013). The algorithm made the diagnosis of migraine even if only photophobia or phonophobia alone was reported provided that the remaining criteria for migraine were fulfilled.

The algorithm was not designed to identify primary thunderclap headache, because this entity requires a meticulous diagnostic workup to exclude secondary conditions. The diagnosis of external pressure headache was also omitted, because the exhaustive explanation of the nature, causes and precipitants of this type of headache was judged to be too tiring for the participant in comparison to its relatively small clinical importance.

The algorithm was composed to make only a single diagnosis per each finished questionnaire except for the case when MOH would be identified. The diagnosis of MOH was additional to the primary (chronic) headache diagnosis. If the participant had more than a single type of headache, (s)he was asked to complete the questionnaire for each type of headache separately, thus avoiding overlooking any co-morbid headaches.

The questionnaire was hosted by Tartu University Hospital's patient website. This is a highly secure website and requires digital identification for access.

4.1.2 Participants

All persons aged 18–65 who had been diagnosed with a definite headache disorder by a neurologist specializing in headaches at Tartu University Hospital's Headache Clinic from February 2014 to March 2015 were invited to fulfil the questionnaire. They were informed of the questionnaire and the purpose of the study by phone. Consenting participants received an e-mail which included a link to the Tartu University Hospital's patient website, a short introduction to the questionnaire, and guidelines for how to complete it.

After answering the questions and before saving the data, patients were once more informed of the purpose of the study and also that by clicking the "Finished" button, they gave their informed consent to participate in the study.

4.1.3 Statistical analysis

The diagnoses made by the neurologists specializing in headaches were compared to the diagnoses made by the algorithm. Sensitivity, specificity, and (prevalence-dependent) positive and negative predictive values of the algorithm were evaluated in the participant sample for each headache diagnosis (ICHD-3 beta second-digit-level diagnosis accuracy by the algorithm was required in order to count the diagnosis as correct) as well as for the larger groups of diagnoses in the study sample (in this case first-digit-level diagnosis accuracy was required to count the diagnosis as correct). After receiving the results of the statistical

analysis of the named parameters of the algorithm using ICHD-3 beta definite criteria, the same parameters were recalculated with added ICHD-3 beta probable diagnostic criteria for the most prevalent groups of diagnoses – namely migraine and tension-type headache. In this case first-digit-level diagnosis accuracy was required to count the diagnosis as correct.

4.2 One-year prevalence of primary headaches in Estonia

4.2.1 Participants

The preselected sample of participants consisted of 3000 subjects aged 18–64 and was derived from Estonian National Registry. It was a random sample of inhabitants of Tartu city and Tartu county demographically representative of Estonian population, and was stratified by gender, age, rural vs urban habitat and marital status.

4.2.2 Survey

The survey was conducted from January 2016 to May 2017. The survey was conducted by telephone or face-to-face by fourteen trained medical students who used a structured questionnaire. If the participant could not be reached by phone on four different occasions, the interviewer visited his/her home address, and if the person was still not found, a note was left that contained a short introduction of the survey and a request to contact the study team.

4.2.3 Questionnaire

The questionnaire described previously under section 4.1.1 was used. The questionnaire was also translated into Russian using forward and backward translations to be used by native Russian speaking participants. If a respondent had more than one type of headache, s/he was asked to describe up to three most bothersome ones.

4.2.4 Caseness and headache diagnoses

According to the data acquired from the questionnaire, the diagnosis of a headache disorder was made by a neurologist specializing in headaches applying the ICHD 3-beta criteria (Headache Classification Committee of the International Headache Society, 2013).

The study was designed to evaluate the prevalences of the following entities: episodic and chronic migraine, episodic and chronic tension-type headache, chronic daily headaches (headache on more than 15 days a month), TACs and

other primary headaches except for primary thunderclap headache and external pressure headache. The latter two were omitted for reasons described under section 4.1.1. The headache had to fit either the definite or probable criteria of ICHD-3 beta to be considered as a case. The criteria were first applied for definite migraine, then definite tension-type headache, then probable migraine, then probable tension-type headache, then definite TACs or definite other primary headaches and finally probable TACs and probable other primary headaches. If a case did not fit under any entity as a probable or definite primary headache syndrome, it was labelled as unidentifiable.

4.2.5 Statistical analysis

The main outcome variables of the study were the one-year prevalences of primary headaches in Estonia. Data analysis was performed using R (R Core Team, 2018). For adjusting the study sample to match the population demographically weighting by age, gender, marital status, habitat and level of education was implemented. Sample weights were calculated using ANES raking algorithm implemented in R package anesrake (Pasek, 2018).

4.3 Applicability of web-based solutions in the epidemiological studies of primary headaches

4.3.1 Survey and participants

A web-based online survey was conducted in parallel to the survey described under sections 4.2.1–4.2.4 also from January 2016 to May 2017.

The participants included in the online survey were Estonian citizens aged 20–64 and they were recruited via internet. For this purpose, an online recruitment campaign was performed. Advertisements for the headache questionnaire described under section 4.1.1 were sent to different online portals and 150 000 e-mails were sent to six most popular e-mail domains in Estonia. The portals and e-mail addresses were chosen by an advertisement company and were aimed at maximum coverage of Estonian digital community. The advertisements and e-mails consisted of a short informative description of a health survey, avoiding any explanation that this was a headache survey in order to minimize participation bias. The advertisements and e-mails also contained a link to the headache questionnaire. The questionnaire was hosted by Tartu University Hospital's server, which provides a highly secure mode for participants' data storage. In order to reach the questionnaire, the participants had to log in with their unique personal Estonian ID cards so that double entries could be traced and managed appropriately. This also secured that only Estonian citizens of the appropriate age were included, since the ID card data include the date of birth of the participants. At the end of the questionnaire there was a more thorough description of the

purpose of the study explaining that it was a headache epidemiology study and making sure that participants, upon being fully informed, had the possibility of leaving the site without saving their data in case they decided not to give their consent. Otherwise, they saved their data by pushing the button „Finished".

In order to encourage participation a lottery was announced on the advertisements and in the e-mails. The lottery draw was performed at the end of the study and two kinds of prizes were awarded to 11 random participants. The prizes were 10 sports-club memberships and 1 tablet-computer.

4.3.2 Questionnaire

The questionnaire described previously under section 4.1.1 was used. In the online study, the questionnaire was self-administered similarly to the original validation process. The participants were required to complete all the questions both of the demographic and diagnostic parts in order to finish the questionnaire, thus avoiding missing data.

4.3.3 Caseness and headache diagnoses

After filling in the headache questionnaire, an ICHD-3 beta (Headache Classification Committee of the International Headache Society, 2013) based diagnostic algorithm was applied and the respondent received one of the following diagnoses: no headache, episodic or chronic migraine, episodic or chronic tension-type headache, one of trigeminal autonomic cephalalgias, one of other primary headaches except for primary thunderclap headache and external-pressure headache, or, in case the described headache did not meet the criteria of any of the aforementioned entities, the unidentified headache was diagnosed. The headache had to fit either definite or probable criteria of ICHD-3 beta to be considered as a case (Headache Classification Committee of the International Headache Society, 2013).

As multiple entries by single participants were expected, the following protocol was developed in order to manage these. In case the results of multiple questionnaire entries were identical, only the first entry was retained in the study. Thus, the multiple entries of the participants made by mistake or to enhance their chances of winning a prize by filling in the questionnaire several times were eliminated. If the results of the questionnaire did not overlap, the following 4 options were possible.

- Firstly, if the age reported by the participant did not match the age by ID (Estonian ID includes the date of birth) the entries were excluded as the participant was filling the questionnaire in under a false identity.
- Secondly, if one entry resulted in a headache diagnosis and another in no headache, the "headache" entry was accepted and "no headache" entries were

excluded, because it is most probable that the "no headache" entries were completed in order to enhance the chances of winning the prize.
- Thirdly, if different entries by a participant resulted in different headache diagnoses that did not exclude each other, they were all accepted as different headaches may occur in one person.
- The fourth option was the case when different entries by a participant resulted in different headache diagnoses that excluded one another – for example the participant had both diagnoses of a chronic and an episodic form of the same headache, or both the probable and definite diagnoses of the same headache. In these cases, the chronic form was accepted and the episodic omitted, or the definite diagnosis accepted and the probable omitted, respectively.

When multiple entries were included from the same participant, s/he was still counted as a single participant having multiple headache cases. In other words, the total number of participants in the sample did not increase, but the number of respective headache cases did.

4.3.4 Statistical analysis

The main outcomes of the online study were the one-year prevalences of primary headache disorders in the study sample. These prevalences were compared to the one-year prevalences of primary headaches in Estonian population acquired from the population-based person-to-person study described under section 4.2. Statistical methods used in both studies were identical. Data analysis was performed using R (R Core Team, 2019). Sample weights were calculated using ANES (American National Election Study (DeBell and Krosnick, 2009)) raking algorithm implemented in R package anesrake (Pasek, 2018) (a standard approach in situations where data need to be simultaneously weighted for multiple demographic criteria). Comparison of the sample proportions was conducted using two-sample test for equality of proportions (with continuity correction).

5. RESULTS

5.1 Diagnostic questionnaire for headache epidemiological research in Estonia

5.1.1 Enrolment of participants

A total of five hundred and eleven headache patients from Tartu University Hospital's Headache Clinic were incorporated in the recruitment process, which started in January 2015 and ended in March 2015. One hundred and forty-five participants were included in final analysis, representing a response rate of 28% (Figure 1).

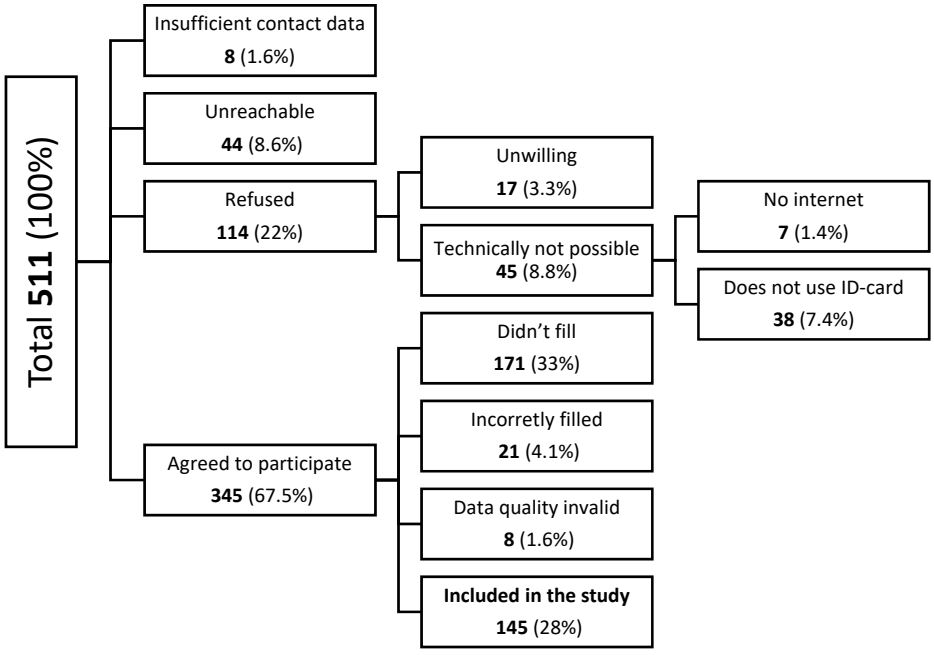

Figure 1. Flowchart of the recruitment of the participants

Demographic characteristics of the final study sample are presented in Table 1.

Table 1. Demographic characteristics of the study participants

Number of participants	145
Age in years: mean	36,3 (24–72)
Gender (% male)	17.2%
Education:	
Primary	2.1%
Secondary	36.6%
Vocational	14.5%
higher education	46.9%
% living in urban area	77.2%

5.1.2 Testing and statistical analysis

Having the headache specialist's diagnosis as the gold standard, the sensitivity, specificity, positive and negative predictive values of the questionnaire and diagnostic algorithm using ICHD-3 beta definite criteria for each diagnosis were calculated. The respective results are depicted in Table 2.

After additionally applying the ICHD-3 beta probable criteria, the specificity values did not decrease markedly but the sensitivity increased considerably for the most prevalent headache diagnosis groups – the sensitivity for all migraines increased from 0.56 to 0.80 and for all tension-type headaches from 0.52 to 0.60; the specificity values remained 0.90 and 0.92 respectively (Table 3).

Table 2. Specificity, sensitivity, positive (PPV) and negative predictive values (NPV) of the questionnaire and diagnostic algorithm for the diagnoses in the study sample

Diagnosis	Number of cases	Specificity	Sensitivity	PPV	NPV
All migraines	**108**	**0.97**	**0.56**	**0.78**	**0.91**
Episodic migraine without aura	74	0.95	0.57	0.48	0.96
Episodic migraine with aura	18	0.99	0.28	0.69	0.96
Chronic migraine	16	0.98	0.38	0.44	0.97
All tension-type headaches	**25**	**0.92**	**0.52**	**0.92**	**0.49**
Episodic tension type headache	19	0.93	0.53	0.92	0.54
Chronic tension type headache	6	0.99	0.5	0.74	0.98
Episodic cluster headache	**2**	**1**	**0.5**	**1**	**1**
All other primary headaches	**8**	**0.98**	**0.50**	**0.30**	**0.99**
Primary exercise headache	1	1	1	1	1
Primary stabbing headache	2	1	0	NA	0.99
Nummular headache	1	0.99	0	NA	NA
NDPH	4	0.99	0.5	0.08	1
Headache attributed to head trauma	**6**	**0.99**	**0.5**	**0.62**	**0.99**
Medication overuse headache	**18**	**1**	**1**	**1**	**1**
Trigeminal neuralgia	**2**	**1**	**1**	**1**	**1**

Table 3. Specificity, sensitivity, positive (PPV) and negative predictive values (NPV) of the questionnaire and diagnostic algorithm for the migraine and TTH diagnoses after incorporating the probable criteria

Diagnosis	Specificity	Sensitivity	PPV	NPV
All migraines	0.90	0.80	0.62	0.96
All tension-type headaches	0.92	0.60	0.93	0.54

5.2 One-year prevalence of primary headaches in Estonia

5.2.1 Study sample composition

Of the 3000 preselected participants 838 (27.9%) had insufficient contact data. Of the contactable sample of 2162 participants 919 (43.2%) refused and 1243 (56.8%) consented to participate in the study. Of those 1243 consenting subjects 28 had missing data or gave unusable answers, so the participating sample consisted of 1215 subjects (Figure 2). Hence, applying the recommendations for methodology of population surveys of headache prevalence from the Global Campaign against Headache (Stovner *et al*, 2014), the participation rate of our study was 56%.

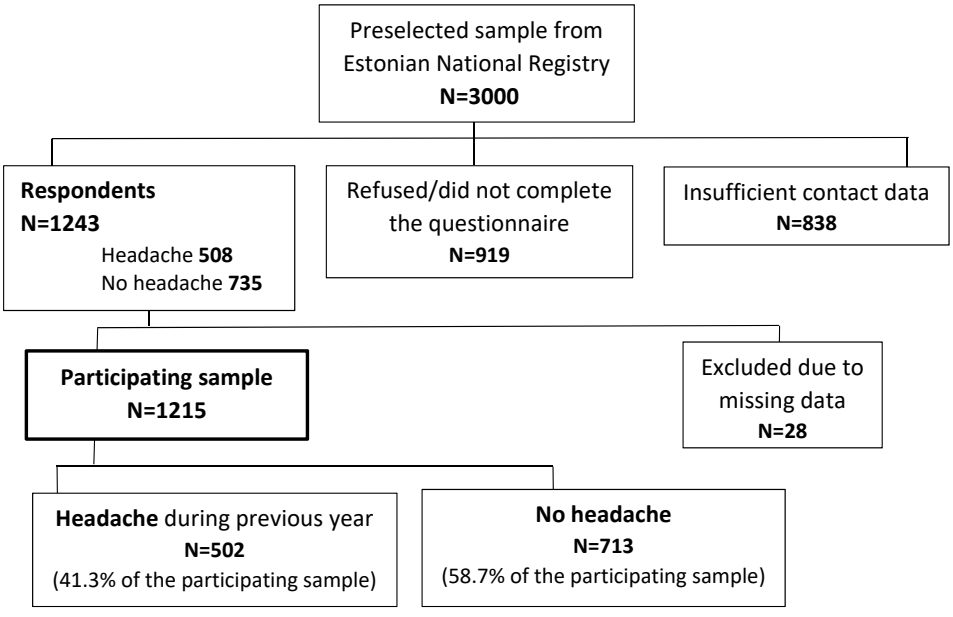

Figure 2. Flowchart of study sample

The demographic characteristics of the participating study sample were statistically significantly different from the overall Estonian population (Statistics Estonia, data from 01.01.2016, accessed 01.03.2018, (Table 4)). Compared to the general population, there were more women and more married people, the proportion of subjects aged 30–49 years was higher, the level of education was higher and the proportion of people living in the rural areas was larger in the study sample. The study sample was adjusted to match the population demographically by weighting by age, gender, marital status, habitat and level of education.

Table 4. Comparison of Estonian population and survey sample for distribution of gender, age, marital status, education and habitat

	General population, 20–64 years, 01.01.2016	**Study sample**	**p-value**
Gender, female (%)	50.4	56.5 (95%CI 53.7–59.2)	<0.001
Age (%)			<0.001
20–29 years	21.8	17.6	
30–39 years	23.1	25.7	
40–49 years	22.2	25.3	
50–59 years	22.1	20.9	
60–64 years	10.5	9.7	
Marital status (%)			<0.001
Married	34.0	44.4 (95%CI 42.0–47.5)	
Not married (incl. single, living with partner, divorced etc.)	66.0	55.6	
Education (%)			<0.001
primary or basic	12.5	6.0	
secondary or vocational	58.0	50.3	
higher	29.5	43.7	
Habitat (%)			<0.001
urban	68.3	61.9	
rural	31.5	36.5	

5.2.2 One-year prevalence of primary headache disorders

Of the participating 1215 respondents, 502 had had headache the previous year. The overall one-year weighted prevalence of headaches was 41% (Table 5). Initially, 34 participants (6.8% out of 502) reported more than one type of headache, and after the final diagnosis was made by a neurologist, it turned out that more than half of them had been describing the same type of headache as two different ones. Thus, only 16 (3.2%) of the participants had reported more than one type of headache.

Table 5. Weighted one-year prevalences of primary headaches in Estonia (weighted by age, gender, marital status, habitat and education)

PRIMARY HEADACHES	Number of cases in participating study sample	Number of cases after weighting	Weighted one-year prevalences (%) with 95% CIs
All headache	**518**	**497.8**	**41.0 (38.2–43.8)**
All migraine	**233**	**215.6**	**17.7 (15.7–20.0)**
• Episodic migraine	221	204.6	16.8 (14.8–19.1)
Definite	93	80.1	6.6 (5.3–8.2)
Probable	128	124.5	10.2 (8.6–12.1)
• Chronic migraine	12	11.0	0.9 (0.5–1.7)
Definite	9	8.8	0.7 (0.4–1.4)
Probable	3	2.2	0.2 (<0.1–0.7)
All tension-type headache	**228**	**218.7**	**18.0 (15.9–20.3)**
• Episodic TTH	213	200.0	16.5 (14.4–18.7)
Definite	154	143.3	11.8 (10.1–13.8)
Probable	59	56.7	4.7 (3.6–6.0)
• Chronic TTH	15	18.7	1.5 (1.0–2.5)
Definite	14	18.1	1.5 (0.9–2.4)
Probable	1	0.6	0.1 (<0.001–0.5)
TACs	**3**	**4.5**	**0.4 (0.1–1.0)**
Other primary headaches	**27**	**29.8**	**2.5 (1.7–3.5)**
Chronic daily headache (headache >15 days a month)	**30**	**32.2**	**2.7 (1.9–3.8)**
Unidentifiable	**21**	**24.0**	**2.0 (1.3–3.0)**

Migraine was reported by 233 respondents and TTH by 228 respondents, and the weighted one-year prevalences were 17.7% and 18.0% respectively. Definite episodic migraine was diagnosed in 93 (weighted one-year prevalence of 6.6%) and probable episodic migraine in 128 respondents (weighted one-year prevalence of 10.2%). Twelve respondents reported having a headache that fulfilled the criteria for chronic migraine (weighted one-year prevalence 0.9%). Definite episodic TTH was diagnosed in 154 (11.8%) and probable episodic TTH was diagnosed in 60 (4.7%) respondents. Chronic TTH was reported by 15 participants (1.5%). Distribution of all migraine and all TTH by age and gender are shown in Figures 3 and 4 respectively.

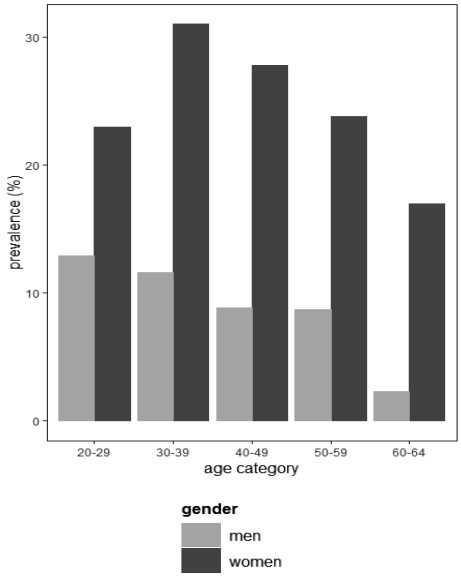

Figure 3. Distribution of all migraine by age and gender

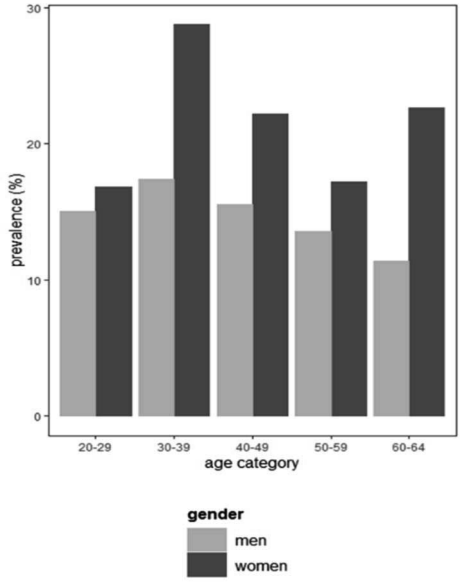

Figure 4. Distribution of all TTH by age and gender

TACs were found in 3 participants, so the weighted one-year prevalence was 0.4% (Table 5). All other primary headaches were reported by 27 participants, having a weighted one-year prevalence of 2.5% (Tables 5 and 6). Chronic daily headache was found in 30 participants (weighted one-year prevalence of 2.7%). This group includes participants with chronic migraine, chronic tension-type headache (Table 5) and the cases that fulfilled the criteria for NDPH (Table 6). The weighted prevalence of unidentified headache type was 2.0% (Table 5).

Table 6. Weighted one-year prevalences of identified other primary headaches in Estonia (weighted by age, gender, marital status, habitat and education)

Other primary headaches	Number of cases in participating study sample	Number of cases after weighting	Weighted one-year prevalences (%)
Primary cough headache	1	0.6	0.1
Primary exercise headache	9	12.2	1.0
Probable primary exercise headache	1	1.1	0.1
Primary headache associated with sexual activity	1	1.0	0.1
Cold-stimulus headache	1	0.9	0.1
Primary stabbing headache	3	3.1	0.3
Nummular headache	4	4.5	0.4
Hypnic headache	1	1.0	0.1
Probable hypnic headache	3	2.9	0.2
NDPH	3	2.5	0.2

5.3 Applicability of web-based solutions in the epidemiological studies of primary headaches

5.3.1 Online study sample composition

During the period from January 2016 to May 2017, five thousand seven hundred and eight entries were made by 5347 individual participants to the online headache questionnaire. Five thousand and thirty-two participants filled in the questionnaire only once, 250 participants made multiple entries, which resulted in identical diagnoses, and 65 participants made multiple entries with differing diagnoses. After addressing the multiple entries according to the protocol described under section 4.3.3, 5363 entries were included and 340 entries were excluded from the final analysis. Of the 5347 participants 3896 (72.9%) had no headache, 1436 (26.8%) had only one type of headache and 15 (0.3%) had more than one type of headache (Figure 5).

The demographic data of the study sample are depicted in Table 7 alongside the data for Estonian population (Statistics Estonia, data from 01.01.2016, accessed 01.03.2018).

The online study sample demographics were statistically significantly different from Estonian population. The proportion of women was higher, participants were younger, there were more married people, the level of education and the proportion of people living in urban areas were higher in the online study sample compared to the general population. Hence, the study sample was adjusted to

match the population demographically by weighting by age, gender, marital status, habitat and education.

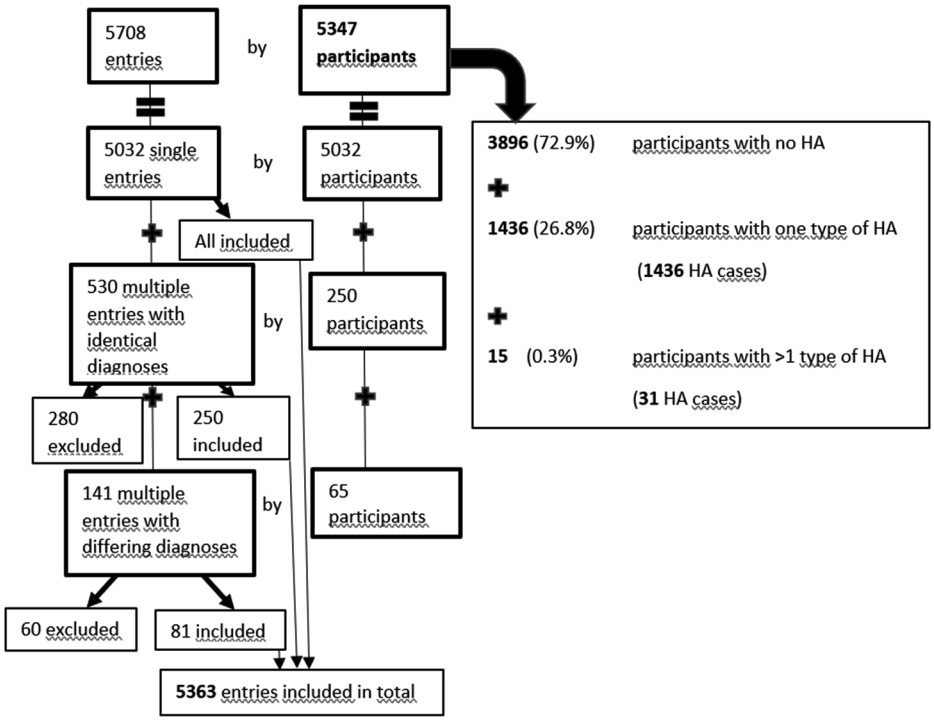

Figure 5. Study sample composition

HA – headache

Table 7. Comparison of Estonian population and online study sample

	General population, 20–64 years, 01.01.2016	**Study sample**	**p-value**
Gender, female (%)	50.4	71.5 (95% CI 70.3–72.1)	<0.001
Age (%)			<0.001
20–29 years	21.8	24.7	
30–39 years	23.1	31.0	
40–49 years	22.2	24.1	
50–59 years	22.1	15.4	
60–64 years	10.5	4.7	
Marital status (%)			<0.001
Married	34.0	36.5 (95% CI 35.2–37.8)	
Not married (incl. single, living with partner, divorced etc.)	66.0	63.5	
Education (%)			<0.001
primary or basic	12.5	3.0	
secondary or vocational	58.0	37.4	
higher	29.5	59.6	
Habitat (%)			<0.001
urban	68.3	71.3	
rural	31.7	28.7	

5.3.2 One-year prevalences of primary headache disorders in the online study sample.

The adjusted prevalences of primary headaches in the online study sample (weighted by age, gender, marital status, habitat and education) are depicted in Table 8.

Table 8. Weighted one-year prevalences of primary headaches in the online study sample

PRIMARY HEADACHES	Number of cases in participating study sample	Number of cases after weighting	Weighted one-year prevalences (%) with 95% CIs
All headache	**1467**	**1234.7**	**23.1 (22.0–24.3)**
All migraine	**508**	**404.1**	**7.6 (6.9–8.3)**
• Episodic migraine	480	375.6	7.0 (6.4–7.8)
Definite	198	159.6	3.0 (2.6–3.5)
Probable	282	216.0	4.0 (3.5–4.6)
• Chronic migraine	28	28.5	0.5 (0.4–0.8)
Definite	12	12.7	0.2 (0.1–0.4)
Probable	16	15.8	0.3 (0.2–0.5)
All TTH	**829**	**703.3**	**13.2 (12.3–14.1)**
• Episodic TTH	781	654.9	12.2 (11.4–13.2)
Definite	558	456.1	8.5 (7.8–9.3)
Probable	223	198.8	3.7 (3.2–4.3)
• Chronic TTH	48	48.4	0.9 (0.7–1.2)
Definite	33	30.2	0.6 (0.4–0.8)
Probable	15	18.2	0.3 (0.2–0.5)
TACs	**2**	**5.3**	**0.1 (0.0004–0.2)**
Other primary headaches	**55**	**57.1**	**1.1 (0.8–1.4)**
Chronic daily headache (headache >15 days a month)	**76**	**76.9**	**1.4 (1.1–1.8)**
Unidentifiable	**43**	**41.8**	**0.8 (0.6–1.1)**

5.3.3 Comparison of the headache prevalences in the person-to-person vs online study samples

The comparison between the adjusted prevalences of primary headaches in Estonian population-based person-to-person study sample described under section 5.2 and in the online study sample (weighted by age, gender, marital status, habitat and education) is depicted in Table 9.

Table 9. Comparison of weighted one-year prevalences of primary headaches in the person-to-person vs online study samples

PRIMARY HEADACHES	Weighted one-year prevalences (%) with 95% CIs in the person-to-person study sample	Weighted one-year prevalences (%) with 95% CIs in the online study sample
All headache	**41.0 (38.2–43.8)**	**23.1 (22.0–24.3)**
All migraine	**17.7 (15.7–20.0)**	**7.6 (6.9–8.3)**
• Episodic migraine	16.8 (14.8–19.1)	7.0 (6.4–7.8)
Definite	6.6 (5.3–8.2)	3.0 (2.6–3.5)
Probable	10.2 (8.6–12.1)	4.0 (3.5–4.6)
• Chronic migraine	0.9 (0.5–1.7)	0.5 (0.4–0.8)
Definite	0.7 (0.4–1.4)	0.2 (0.1–0.4)
Probable	0.2 (<0.1–0.7)	0.3 (0.2–0.5)
All TTH	**18.0 (15.9–20.3)**	**13.2 (12.3–14.1)**
• Episodic TTH	16.5 (14.4–18.7)	12.2 (11.4–13.2)
Definite	11.8 (10.1–13.8)	8.5 (7.8–9.3)
Probable	4.7 (3.6–6.0)	3.7 (3.2–4.3)
• Chronic TTH	1.5 (1.0–2.5)	0.9 (0.7–1.2)
Definite	1.5 (0.9–2.4)	0.6 (0.4–0.8)
Probable	0.1 (<0.001–0.5)	0.3 (0.2–0.5)
TACs	**0.4 (0.1–1.0)**	**0.1 (0.0004–0.2)**
Other primary headaches	**2.5 (1.7–3.5)**	**1.1 (0.8–1.4)**
Chronic daily headache (headache >15 days a month)	**2.7 (1.9–3.8)**	**1.4 (1.1–1.8)**
Unidentifiable	**2.0 (1.3–3.0)**	**0.8 (0.6–1.1)**

The percentage of headache sufferers in general was considerably smaller in the online study sample. However, among the participants who had headaches, the proportions of different headache diagnoses were similar in the two studies (Table 10 and Figure 6) with only the proportions of episodic migraine and episodic tension-type headache being statistically different. There were proportionally less migraine and more tension-type headache sufferers in the online study sample compared to the population-based person-to-person study sample in Estonia.

Table 10. Comparison of proportions of different primary headache diagnoses among headache sufferers in the person-to-person and online study samples

Primary headaches	Weighted number of cases in Estonian population based person-to-person sample survey	Proportions of diagnoses among headache sufferers in the population based person-to-person sample (%)	Number of cases after weighting in the online sample	Proportions of diagnoses among headache sufferers in the online sample (%)	p-value for the proportions being different (χ2 tested)
Episodic migraine	204.6	42	375.6	31	< 0.001
Chronic migraine	11	2	28.5	2	1
Episodic TTH	200	41	654.9	54	< 0.001
Chronic TTH	18.7	4	48.4	4	0.96
TACs	4.5	1	5.3	1	0.41
Other primary headaches	29.8	6	57.1	5	0.31
Unidentifiable	24	5	41.8	3	0.21

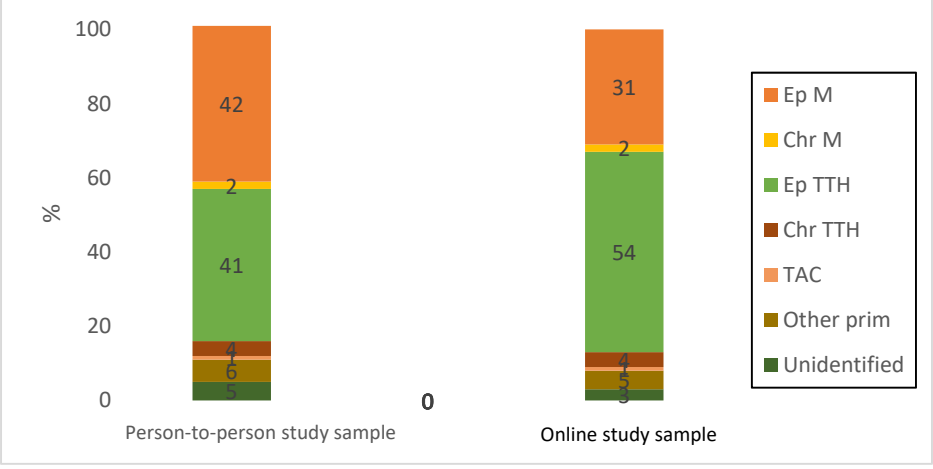

Figure 6. Proportions of different primary headache diagnoses among headache sufferers in the person-to-person and online study samples

Ep M: episodic migraine; Chr M: chronic migraine; Ep TTH: episodic tension type headache; Chr TTH: chronic tension type headache; Other prim: other primary headaches; TAC: trigeminal autonomic cephalalgias.

6. DISCUSSION

6.1 Diagnostic questionnaire for headache epidemiological research in Estonia

The main objective of the first part of the study (paper I) was to test the developed online questionnaire with its digital algorithm described in sections 4.1 and 5.1 before using it in further epidemiological research.

The main reason the headache questionnaire was originally composed as an online version was the hypothesis that implementing web-based solutions could potentially provide opportunities for gaining data representative of a general population in a more time and resource efficient manner than the traditional person-to-person epidemiological studies in headache prevalence. It must be acknowledged that such an approach is reasonable only within an appropriate setting like Estonia, where the availability of online solutions and their real utilization is sufficiently high and has already become a natural part of everyday life in the country (International Telecommunication Union, 2017; European Commission, 2019) and the extensive majority of the general population (especially those under investigation – that is, 18–64-year-olds) are actively and comfortably in touch with e-solutions on an everyday basis.

The questionnaire and the diagnostic algorithm applied (at the time of the first part of the study) the latest ICHD-3 beta criteria to diagnose a wide spectrum of headache disorders – including virtually all the primary headache disorders except for primary thunderclap headache and external pressure headache, which is rather a rare case in headache epidemiological studies published to the date.

Another strength of the questionnaire is that it is fairly simple and easy to complete. This is supported by the finding that only about 4% of the participants filled the questionnaire in incorrectly, either by giving illogical responses or by not answering all the compulsory questions. One more advantage of the online questionnaire is that since digital identification is required of the participant, it enables the collection of personalized data, which in turn permits the elimination of repeated data entries and the acquisition of accurate prevalence estimates of primary headache disorders.

The quality control of the referent headache cases of the first study was very good as all participants were previously consulted and diagnosed with a headache disorder by a Tartu University Hospital's Headache Clinic specialist.

The diagnostic algorithm was at first designed to apply strictly the ICHD-3 beta definite criteria – this is why the questionnaire initially had very high specificities. Sensitivities for some of the headache diagnoses in the study sample, however, turned out to be low. This especially relates to the sensitivities for episodic migraine with aura, chronic migraine, primary stabbing headache, and nummular headache. One of the reasons the algorithm could not detect the diagnosis in the case of migraines was related to the participants reporting their headache duration without treatment to be less than four hours, which automati-

cally excluded the definite migraine diagnosis, according to ICHD-3 beta. In some cases, the migraine diagnosis was not identified, because the participants did not report any accompanying symptoms, although these were clearly stated in their headache specialist medical history. In some instances, the algorithm did not recognise a definite diagnosis, because the case itself was atypical and thus undetectable by the strict criteria, although the physician's diagnosis was established as a definite primary headache. Excluding the previously mentioned values, the sensitivities for other diagnoses were 0.5 or above. Similar sensitivity values (53.8–57.2%) were also achieved by Wilbrink *et al* for the LUCA and QATCH online questionnaires (Wilbrink *et al*, 2013). The authors concluded that such an approach is acceptably accurate and reliable for a certain part of epidemiological studies with specific purposes. However, this is not the case in population-based epidemiological studies. In addition, another aspect has to be taken into account when interpreting the calculated sensitivity values. The present statistical methodology for calculating sensitivity values requires an exact knowledge of the prevalence rates of the disorder(s) in the particular settings where the study is being performed. Since no such data for Estonia were available, the prevalence rates needed for the analysis were adopted from studies performed elsewhere. The latter ones, however, may vary to a considerable extent depending on the specific headache disorder (Stovner *et al*, 2006; Stovner *et al*, 2007, Stovner and Andree, 2010). Hence, based solely on the adopted prevalence rates, the real sensitivity values might be somewhat different from the presented ones.

As applying only definite ICHD-3 beta criteria for different headache disorders resulted in unacceptably low sensitivity estimates, the ICHD-3 beta criteria for probable diagnoses were also incorporated in the algorithm. This increased sensitivity considerably (for example, in the case of migraine, from 0.56 to 0.80) by detecting those cases that did not fulfil the definite diagnostic criteria but in real life lead to the clinical diagnosis by the physician. Including criteria for probable headache diagnoses helps to address another important aspect in headache epidemiological studies – it minimizes the influence of recall bias (patients forgetting to report one or several headache characteristics) on the results, which in turn brings the prevalence rates closer to real ones. Based on these findings, it can be suggested that strictly applying the ICHD-3 beta definite criteria within the epidemiologic studies can lead to an underestimation of true prevalence values of primary headache disorders. This is in concordance with findings from earlier studies (Lanteri-Minet *et al*, 2005; Stovner and Andree, 2010).

Limitations of the study testing the online questionnaire must be mentioned. The response rate of the study is not high (28%). However, it is considered acceptable. For example, when validating the QATCH online questionnaire, Wilbrink *et al* had the same variable at 20% (Wilbrink *et al*, 2013). A rather low response rate also contributed to the study sample being relatively small and all the diagnoses that the algorithm was designed for not being covered. For instance, no participants with rather rare headache disorders such as chronic CH, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks, primary cough headache, primary headache associated with sexual activity, cold-

stimulus headache, or hypnic headache could be enrolled. For some entities, namely episodic CH, primary exercise headache, nummular headache, primary stabbing headache, and trigeminal neuralgia, there were only a few participants, so the conclusiveness for these diagnoses is not strong. This is also why the sensitivities for nummular headache and primary stabbing headache were very low.

Secondly, it must be acknowledged that the sensitivities and specificities have been calculated on a sample of "pre-educated" patients, as they had been to a headache specialist consultation previously. This can be an important source of information bias, since pre-educated participants are more likely to recognise the different aspects (like the presence or lack of accompanying symptoms or duration of the episodes) of their headaches. Thus, the sensitivities and specificities of the questionnaire and the acquired prevalence rates of different headache disorders may decrease in case the questionnaire is applied to the general population, leading to possible underestimation of headache prevalence.

In conclusion, the online questionnaire, especially after adding the ICHD-3 beta criteria for probable headache diagnoses to the diagnostic algorithm, had acceptably high specificity and sensitivity for the main entities in headache epidemiology – namely migraine and TTH, to be applied in the further study.

6.2 One-year prevalence of primary headaches in Estonia

The aim of the second part of the study (paper II) was to estimate the one-year prevalences of primary headache disorders in adult population in Estonia. This was the first headache prevalence study conducted in this country.

The general one-year prevalence of headache in Estonia (41%) is somewhat lower than the mean prevalence in Europe (53%) (Stovner and Andree, 2010). It is comparable to the headache prevalences reported in Georgia (Katsarava *et al*, 2009) and Italy (D'Alessandro *et al*, 1988) and higher than the prevalences in Sweden (Molarius *et al*, 2006), Greece (Mitsikostas *et al*, 1996) and France (Henry *et al*, 2002).

The one-year prevalence of both probable and definite episodic migraine combined in Estonia (16.8%) is comparable to the mean prevalence of migraine in Europe (14.7%) (Stovner and Andree, 2010), being closest to the respective one-year prevalences in France (Henry *et al*, 2002), Croatia (Zivadinov *et al*, 2001), the Netherlands (Launer et al, 1999), Georgia (Katsarava *et al*, 2009) and Moldova (Moldovanu *et al*, 2007).

There are extreme variations in the prevalences of episodic TTH across regions and cultures worldwide (Stovner *et al*, 2007; Sahler, 2012). The estimated one-year prevalence of episodic TTH in Estonia (16.5%) appears to be about three times lower than the mean prevalence in Europe (62.6%) (Stovner and Andree, 2010). The variation of the prevalence of TTH within Europe itself is wide too – ranging from 18% in Moldova (Moldovanu *et al*, 2007) to 86.5% in Denmark (Lyngberg *et al*, 2005). The differences in methodological approaches across

studies, diagnostic overlap with probable migraine, variability in headache awareness and socioeconomic situation across countries or unknown genetic or environmental factors are the suspected reasons behind this phenomenon (Steiner *et al*, 2013; Stovner *et al*, 2014; Sahler, 2012). The low one-year prevalence rate of episodic TTH in this study could be due to two types of factors – sociocultural and methodological. Firstly, in Estonia it is not customary to complain about milder pain or headaches nor to consider them as diseases or noteworthy health issues, thus the infrequent or subtler forms of TTH might not be paid attention to and go unreported. Additionally, in case of milder headaches as TTH generally are, there is always the problem of recall bias and thus infrequent faint headaches might simply not be remembered over the period of a year.

Secondly, there is a set of possible methodological reasons for this low prevalence of episodic TTH in this study. As described under section 4.2.4 previously, both definite and probable categories for both migraine and TTH were included. If a case fulfilled both criteria for migraine and TTH the first was favoured over the latter. This means that in cases of doubt the prevalence of TTH could be slightly underestimated in favour of the prevalence of migraine. Another methodological aspect, which is generally accepted as a large problem in epidemiological studies, is the occurrence of multiple headache types in the same subject (Stovner *et al*, 2014). The respondents tend to report the most bothersome headache, despite of being offered the opportunity to describe more than one. Thus, respondents who have comorbid migraine with TTH, might report the former and omit the latter. This is also supported by the data from this study, since the proportion of participants reporting more than one type of headache was small (6.8%) and the real comorbidity after the cases had been diagnosed was even two times smaller. As under-reporting is not the case in clinical experience, it again points to the possibility of underestimation of milder comorbid headache disorders, most prominently infrequent episodic TTH. Similar problems with underestimating the prevalence of episodic TTH in case of comorbid migraine has been reported before (Zwart *et al*, 2004). Lastly, one of the possible methodological reasons for underestimating the prevalence of episodic TTH is due to the limitations related to the screening question used in this study, which will be discussed further on in this section.

Aside from the episodic TTH, the prevalence of chronic TTH in this study (1.5%) is comparable to that of Europe (3.3%) (Stovner *et al*, 2010), being the closest to Denmark (0.9%) (Russell *et al*, 2006) and Germany (1.3%) (Pfaffenrath *et al*, 2009).

The mean one-year prevalence of CDH (headache on ≥ than 15 days per month) has been reported to be around 4% in Europe (Stovner *et al*, 2010), however, the prevalences vary across regions being somewhat lower in Western Europe (Rasmussen *et al*, 1991; Henry *et al*, 2002; Wiendels *et al*, 2006; Grande *et al*, 2008) and higher in Eastern Europe (Lyngberg *et al*, 2005; Katsarava *et al*, 2009; Rastenytė *et al*, 2017). The finding of the one-year prevalence of CDH of 2.7% in this study is closer to the Western European prevalence.

TACs are rare and therefore it is impossible to validate a questionnaire with sufficient power to make a reliable diagnosis by that alone. However, there were three cases in this study sample in which the reported headaches fulfilled the definite or probable criteria for TACs, corresponding to the one-year prevalence of 0.4%, which is comparable to the previous studies on the prevalence of CH in European countries (Sjaastad and Bakketeig, 2003; Torelli *et al*, 2005; Ekbom *et al*, 2006; Katsarava *et al*, 2007 and 2009; Stovner *et al*, 2010).

The same problem of rarity and lack of a reliably validated questionnaire exists when it comes to other primary headaches. Data on the prevalences of these entities is even scarcer. The Bruneck Study from Northern Italy estimated the one-year prevalence of all other primary headaches combined to be 1.7% (Schwaiger *et al*, 2009). This is comparable to our finding – 2.5% of our participants reported different headaches, which did not fulfil ICHD 3-beta criteria for neither migraine nor TTH but did so for either definite or probable criteria for the entities described in section 4 of the ICHD 3-beta.

A slight proportion of the differences in the prevalences found in this study as compared to the previous headache studies could have occurred due to the fact that the ICHD 3-beta criteria were used to diagnose the cases whereas the previous studies used the ICHD 2.

This person-to-person prevalence study has several limitations. Firstly, the participation rate of the study was 56%. This is a moderate response rate (Stovner *et al*, 2014). It can be speculated that in addition to Estonian people being rather reserved and conservative when it comes to communication on health-related topics, one of the reasons for refusing to participate in the study is the limited knowledge about headaches and their impact in the general population. Hence, the problem is underappreciated, and people are not motivated enough to participate in such a study. Another reason for refusal to participate particularly over the phone may be the negative influence of advertisement by phone, which is rather prevalent in Estonia. It is thus possible that people are put off by surveys that are carried out over the telephone. Quite a large proportion of the preselected sample (27.9%) could not be reached because of insufficient contact data. It could partly be due to the fact that the Estonian National Registry was last updated in 2011 when the latest census was conducted, while this survey started in 2016. This leaves a time gap of five years during which a proportion of contact data had inevitably expired. It is also possible that of the 838 people whom were considered as having insufficient contact data, a number would actually have qualified as non-responders either because they did not want to answer a phone call from an unknown number, or because they chose not to contact the study team after they received the note that was left to their home address by one of the investigators. The size of the proportion of these subjects is impossible to determine retrospectively and it is a possible source of selection bias. It must also be taken into account that people with headache are more willing to participate in a headache study. Given that 43.2% of the contactable sample refused to participate in the study, a possible interest bias that may lead to an overestimation of the true prevalence of headache disorders can not be totally excluded.

Secondly, a possible source of bias was created by using a questionnaire that was validated in a clinical setting as discussed previously under section 6.1. This again created the risk of underestimating the true prevalences in the population, since headache clinic patients are pre-educated and know how to answer the questions more precisely. In order to compensate for these differences between the validation sample and the general population, the interviews were carried out by medical students so the participant could ask for clarification if in doubt or confused about the questions asked. Thus, although during the aforementioned validation study the questionnaire was self-administered and in the population-based epidemiological study the questionnaire was administered by telephone or face-to-face by medical students, this would not lead to significant over- or underestimation, because person-to-person interview gives the participant the possibility to ask specifying questions in case of doubt resulting in more reliable responses than with a self-administered questionnaire.

Lastly, one source of possible underestimation of the prevalences can be hidden within the screening question. The specific wording was used to avoid contamination of the data by secondary headaches, however, it has been shown that such a non-neutral screening question may produce false negatives (Stovner *et al*, 2014). As mentioned before in this section, this can also be one of the reasons why the prevalence of episodic TTH in our study was lower than in other countries nearby. The subjects were asked if they had had „recurrent" headaches, and it may be suspected that people with infrequent and milder headaches do not consider these attacks as recurrent and thus do not report them. This may cause the underestimation of all types of headaches, but most of all episodic TTH, which is by definition a milder and less bothersome headache (Zwart *et al*, 2004).

The main strength of this population-based person-to-person study is that it estimated the one-year prevalence of almost all primary headaches in Estonia, including migraine and TTH as the socioeconomically most bothersome entities as well as the rare TACs and other primary headaches. While the previously discussed uncertainties cannot be denied in the estimates, the results of this study may be considered as representative of Estonian population aged 18–64 years. The results are comparable to previous findings in other European countries, except for the episodic TTH. Another strength of the study is the low proportion of unidentified headaches (2%) in the sample. Lastly, the most up-to-date classification for headache case ascertainment was used, while the vast majority of prevalence studies published in recent years were based on the previous – ICHD-2 – classification.

6.3 Applicability of web-based solutions in the epidemiological studies of primary headaches

The third part of the study was aimed to experimentally and evidentially address the question if web-based approach to the epidemiological studies of primary headache disorders could be useful, and what pitfalls there might be expected. The comparison between the online and person-to-person survey methods would be optimal, the most correct and informative only if both surveys were performed within the same population during the same time period. This was the case here, as the online study described under sections 4.3 and 5.3 was compared to the person-to-person study described under sections 4.2 and 5.2. Online solutions have been used in headache research previously (see section 2.9) but there have been no attempts to conduct an online survey for all primary headache epidemiology involving a whole country.

One of the considerations in favour of online approach to epidemiological studies is time. Although the online headache questionnaire was available for fifteen months, it could be noticed that most of the entries were made in close temporal connection to the launches of the online advertisement and e-mail campaigns with most of the entries (n=4082, 76% of total) made during 3 months' time after the release of the campaign. This means that compared to the traditional methods of epidemiological studies it presents a much faster and cost-effective means of data collection. Additionally, the online study sample was considerably larger than the sample obtained in the offline person-to-person study that was carried out in parallel. Hence the power of the study is also bigger and statistical corrections can be made with smaller error. This is one of the biggest benefits of online surveys – the acquisition of large samples with less consumption of time and resource.

The prevalence of all headache in the online study sample after adjusting it to the general population by age, gender, marital status, habitat and education was only 23.5% – almost 2 times smaller than the prevalence of all headache in the population-based random sample person-to-person survey performed in parallel. This is likely to mean that the online survey was significantly biased towards the people without headache. We speculate that one of the reasons this could have occurred was the selection bias created by the lottery that was originally intended to enhance participation. Since the potential reward was a gym membership, it is possible that physically more active individuals may have been more likely to participate, reducing the prevalence of headaches (Amin *et al*, 2018). It is also possible that a proportion of the participants did not take the trouble to fill in the questionnaire truthfully even if they had had a headache during the previous year and simply took the easy way out by saying they had not in order to be able to participate in the aforementioned lottery. Although participants not admitting to having had a headache could not be totally excluded in the person-to-person survey, it is definitely more likely to have occurred in the web-based approach.

When omitting the participants without headache and looking at the proportions of primary headache diagnoses among those who reported headache in the online study, they are surprisingly similar to those found in the population based person-to-person random sample survey in Estonia (Figure 6, Table 10). The only statistically different proportions were those of episodic migraine and episodic TTH, whereas the proportions of chronic migraine, chronic TTH, TACs, other primary headaches and even unidentified headaches were almost identical. Furthermore, even the proportions of the statistically different episodic TTH and episodic migraine are still similar to the proportions of their counterparts in the population-based person-to-person random sample study in the respect that these are still the largest and most prevalent diagnoses of primary headaches in the samples: in both studies, episodic TTH and episodic migraine together comprise 83% and 85% of the primary headaches, respectively. The proportion of episodic TTH is larger and the proportion of episodic migraine is equally smaller in the online study compared to the person-to-person study. One of the reasons for this discrepancy might be the fact that in the population-based person-to-person study the questionnaire was administered face-to-face or by telephone interviews whereas in the online study the questionnaire was completely self-administered. Since migraine diagnosis requires more detail (presence of accompanying symptoms etc) these nuances might be missed when the questionnaire is self-administered as opposed to the situation where the participant can ask clarifications from the interviewer. On the other hand, most of the headache prevalence studies so far have demonstrated that TTH usually is more prevalent than migraine in any given population (Stovner *et al*, 2007; Stovner and Andree, 2010). As described previously, the prevalence of episodic TTH in the population-based person-to-person random sample study (18%) is exceptionally low when compared to other countries in the same North-Eastern European region. The reasons for this possible underestimation were also discussed in the previous section. However, this raises the question of whether the online study could have reflected the proportions of primary headache disorders in the population even more truthfully. Nevertheless, it is apparent that underestimation of headache prevalence would be one of the most troubling issues of online prevalence studies.

Another important factor, that the third part of the study underlined, is the necessity of having the participants identify themselves by some unique ID method. The 671 multiple entries by the same participants in the online study (about 12% of all the entries) certainly point to the fact that in such web-based surveys it is vital to have an identification method that would grant the means to manage the situation, especially where multiple entries increase the chances of winning a prize for participants. This again provides evidence that if lotteries and other similar "stimulating packages" are to be used to boost participation, it must be applied with utmost care to minimize the inevitable bias.

The main limitations of the online study are related to the sampling methods. Valid conclusions of the population of interest (in this case Estonian population of 20–64 years of age) require probability sampling, where all members of the population have an initial probability of being selected to the study sample

(Stovner *et al*, 2014). In our case it means that since almost about 87% of 16–74-year-olds in Estonia use internet on daily basis (International Telecommunication Union, 2017), about 13% of the population would be isolated from the possibility of being invited to a study when conducted online. However, there is no information about the age distribution of the non-users within this 13%. It is highly probable that most non-users are in the older age group. Since the online study sample's upper age limit was 64 years, it is quite possible that the actual percentage of internet users within the targeted age-population is even higher than 87%, but this remains speculative due to lack of respective data.

The hypothesis that high internet coverage among the general population in Estonia would be a factor sufficient enough for obtaining a representative sample by the chosen method of access and engagement was tested. The analysis of the demographic data of the sample evidentially overruled this hypothesis. The sample of 5347 participants was statistically significantly different form the general population of Estonia – it consisted of a younger, more educated and more urban group of people and there were more women than men among the participants. The smallest difference, although statistically significant, was in the marital status of the participants compared to the general population – there were more married people in the study sample. This shows that simply by addressing the digital community based on the most popular sites and domains does not grant a representative sample of general population even in the countries with highly developed information technology and in order to obtain representative samples in the future online epidemiological studies the methods of sampling, access and engagement must still be more conservative (Stovner *et al*, 2014). There can be several possible solutions: the targeted invitation to the study could be linked to banking systems, e-health registries or e-mail addresses from national population registries in countries that use corresponding solutions extensively among adult population.

The evidence provided by the comparison of the online and person-to-person studies should be considered when planning further research and generating guidelines for using web-based approaches in headache epidemiology.

7. CONCLUSIONS

1. The developed and tested online headache questionnaire had reasonably high specificity and sensitivity for the main entities in headache epidemiology – namely migraine and TTH, to be acceptable for using the tool in an epidemiological study. Strictly applying the ICHD-3 beta definite criteria within the epidemiologic studies lead to an underestimation of true prevalence values of primary headache disorders, and probable criteria should be included to increase the sensitivity of questionnaires.

2. The one-year prevalences of primary headache disorders in Estonia are comparable to previous findings in other European countries, except for the episodic TTH. The low prevalence of episodic TTH is most probably an underestimation due to limitations of the study. The findings of the study mean that, like in other countries, primary headaches in Estonia are an important cause of morbidity, loss of quality of life and personal suffering as well as a prominent socioeconomic burden.

3. In the face of an already extensive and rapidly increasing usage of internet and IT-solutions among the general population, online headache epidemiology research could be a time- and resource efficient alternative in technologically developed countries. In addition to the possibility of obtaining larger study samples in relatively short time periods, the IT solutions are capable of providing participant identification methods that enable avoiding data contamination and are able to distinguish the proportions of most primary headache disorders among the headache sufferers. However, further research is needed to find more reliable methods of online access and engagement to gain representative samples and overcome the pitfalls of bias and most probably underestimation of headache prevalence in web-based epidemiological research.

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9. SUMMARY IN ESTONIAN

Esmaste peavalude levimus Eestis ning internetipõhise lahenduse kohaldatavus peavalude epidemioloogia alases uurimistöös

Esmased peavalud on iseseisvad haigused, millel on erinevad, kuigi mitte lõpuni teadaolevad patofüsioloogilised mehhanismid, ning mida ei põhjusta mingi muu haigus või tervisehäire. Esmaste peavalude hulka kuuluvad migreen, pingetüüpi peavalu, trigeminaalautonoomsed tsefalalgiad ning muud esmased peavalud. Need neli suurt kategooriat hõlmavad omakorda mitmeid erinevaid nimetatud peavalude alatüüpe ning ka iseseisvaid diagnostilisi üksusi (Rahvusvahelise Peavalude Seltsi Peavalude Klassifikatsiooni Komitee, 2018).

Esmased peavalud põhjustavad märkimisväärset isiklikku kannatust ning elukvaliteedi langust, kuid on olulised mõjutajad ka rahvatervise seisukohast ning arvestatava ühiskondliku koorma allikaks (Steiner jt, 2014; *Global Burden of Disease*, 2015; Messali jt, 2016; Saylor ja Steiner, 2018). Migreen ja pingetüüpi peavalu on mõlemad kuue kõige levinuma haiguse hulgas maailmas ning migreen on teisel kohal puudega elatud aastate põhjusena (Vos jt, 2017).

Epidemioloogilise uurimustöö tulemused loovad aluse haigusmustrite, haigusest põhjustatud isikliku ja ühiskondliku koormuse ja maksumuse ning tervishoiusüsteemi vajaduste hindamiseks ühiskonnas (Steiner jt, 2013; Stovner jt, 2014). Esmaste peavalude epidemioloogiat puudutavaid andmeid on maailmas viimasel kahel aastakümnel järjest rohkem kogunenud (Stovner jt, 2007; Stovner ja Andree, 2010; Maailma Tervishoiu Organisatsioon ja *Lifting The Burden*, 2011; Saylor ja Steiner, 2018), kuid mõnes regioonis on tühimikud ikkagi märgatavad. Kõikide peavalude keskmine aastane levimus Euroopas hinnatakse 53%-le, migreeni keskmine aastane levimus on 14,7% ja pingetüüpi peavalul 62,6% (Stovner ja Andree, 2010). Trigeminaalautonoomsete tsefalalgiate aastane levimus on siiani avaldatud andmetel 0.05% (Fischera jt, 2008) ning kõikidel muudel esmastel peavaludel 1,7% (Schwaiger jt, 2008). Eesti kohta ei ole esmaste peavalude levimuse andmeid varem avaldatud.

Suured populatsioonipõhised epidemioloogilised uuringud on tavaliselt ressursi- ning ajakulukad (Stovner jt, 2014). Samas on praegune kiire digiühiskonna areng loomas potentsiaalseid eeldusi otsimaks alternatiivseid epidemioloogilistes uuringutes rakendatavaid veebipõhiseid meetodeid, mis võimaldaksid järjest avarduvaid infotehnoloogilisi võimalusi kasutades aja- ning ressursimahtu vähendada. Kindlasti oleks selline lähenemine võimalik peavalude epidemioloogilistes uuringutes, arvestades, et enamike esmaste peavalude puhul on võimalik peavalu tüüpi määrata uuritava kaebuste ning anamneesi alusel ilma instrumentaalsete uuringute vajaduseta (Mitsikostas jt, 2015).

Eesti on maailmas üks juhtivaid riike interneti ning veebipõhiste lahenduste kasutamise osas kodumajapidamises (Rahvusvaheline Telekommunikatsiooni Liit, 2017). 2019. aastal oli Eesti Euroopa Liidu liikmesriikide seas kaheksandal kohal digitaalse majanduse ja ühiskonna indeksi poolest (Euroopa Komisjon,

2019), mis on näitaja, mis arvestab Euroopa riikide digitaalse sooritusse erinevaid tahke nagu digitaalne ühenduvus, inimeste digitaalne hõlmamine ja oskused, veebiteenuste kasutamine, digitaalse tehnoloogia integratsioon ühiskonnas ning digitaalsed avalikud teenused.

Nimetatud asjaolud loovad head eeldused katsetamaks veebipõhise lähenemise rakendamist peavalude epidemioloogiliseks uurimiseks just Eestis.

Uurimuse eesmärgid

Antud uurimustöö eesmärkideks olid esmaste peavalude epidemioloogilise uurimuse jaoks diagnostilise küsimustiku koostamine ning testimine, esmaste peavalude aastase levimuse määramine 20–64-aastaste täiskasvanute seas Eestis ning veebipõhise lahenduse kohaldatavuse hindamine peavalude epidemioloogia alases uurimistöös, võrreldes veebipõhiselt teostatud uuringu ning populatsioonipõhise epidemioloogilise uuringu tulemusi.

Uuritavad ja meetodid

Uurimustöö kiitis heaks Tartu Ülikooli inimuuringute eetika komitee (load nr. 242T-11 ja nr. 252T-15). Kõik uuritavad andsid kirjaliku või digitaalse informeeritud nõusoleku uuringus osalemiseks.

1. Peavalude epidemioloogilise uuringu küsimustiku koostamine ja testimine (I artikkel)

Koostati veebipõhine peavalude küsimustik koos diagnostilise algoritmiga. Viimane tugines Rahvusvahelise Peavalude Klassifikatsiooni 3. beetaversiooni diagnoosikriteeriumitele ning selle eesmärgiks oli küsimustiku vastuste alusel diagnoosida enamusi esmaseid ja üksikuid teiseseid peavalusid. Kõiki 18–65 aasta vanuseid patsiente, kellel oli Tartu Ülikooli Kliinikumi peavalukliinikus peavaluarsti poolt veebruarist 2014 kuni märtsini 2015 diagnoositud kindlat tüüpi peavalu, paluti küsimustikku täita. Algoritmi poolt pakutud peavalu diagnoosi võrreldi peavaluspetsialisti poolt püstitatud diagnoosiga, et hinnata küsimustiku ja algoritmi sensitiivsust, spetsiifilisust, postiivset ja negatiivset ennustusväärtust.

2. Esmaste peavalude aastane levimus 20–64-aastastel täiskasvanutel Eestis (II artikkel)

2016. aasta jaanuarist kuni 2017. aasta maini läbi viidud uuringus kasutati Eesti rahvastikuregistrist saadud 3000 uuritavaga juhuvalimit, mis oli soo, vanuse, elukoha (maal või linnas) ning perekonnaseisu järgi kihitatud ning vastas Eesti üldpopulatsiooni vastavatele näitajatele. Uuritavad olid 20–64-aastased ning elasid Tartu linnas või Tartu maakonnas. Uuritavatega kontakteerusid eelnevalt uuringu metoodika osas koolitatud meditsiiniteaduste valdkonna üliõpilased, kes palusid uuritavatel kas telefonitsi või näost näkku vastata eelnevalt kirjeldatud peavaluküsimustikule. Uuritaval lubati kirjeldada kuni kolme kõige tülikamat peavalu tüüpi. Küsimustikke analüüsis neuroloog, kes saadud vastuste alusel ning Rahvusvahelise Peavalude Klassifikatsiooni kolmanda beetaversiooni

kriteeriumitele toetudes määras peavalu kirjeldanud uuritavate peavalu tüübi. Eristati järgmisi diagnoosikategooriaid: episoodiline ja krooniline migreen, episoodiline ja krooniline pingetüüpi peavalu, krooniline igapäevane peavalu (peavalu ≥15 päeval kuus), trigeminaalautonoomsed tsefalalgiad ning muud esmased peavalud. Kirjeldatud peavalu pidi täitma eelmainitud kategooriate kindlaid või võimalikke diagnoosikriteeriume. Kui peavalu ei täitnud ühegi kategooria tingimusi, diagnoositi teadmata peavalu. Uuringu valimit kaaluti uuritavate vanust, sugu, elukohta, haridustaset ning perekonnaseisu arvestades, et uuringu valim vastaks demograafiliste andmete osas Eesti üldpopulatsioonile. Saadud tulemuste alusel kalkuleeriti esmaste peavalude aastane levimus 20–64-aastastel täiskasvanutel Eestis.

3. Veebipõhise lahenduse rakendatavus esmaste peavalude epidemioloogilises uurimistöös (III artikkel)

Eelnevalt kirjeldatud veebipõhist peavaluküsimustikku kasutades viidi 2016. aasta jaanuarist kuni 2017. aasta maini läbi internetipõhine uuring 20–64-aastaste Eesti kodanike seas. Uuritavad värvati interneti teel, teavitades neid küsimustikust Eesti digitaalses kogukonnas kõige populaarsemate portaalide ning 150 000 e-maili kaudu. Saadud valimis arvutati esmaste peavalude aastased levimused, mida võrreldi eelnevalt kirjeldatud populatsioonipõhises uuringus leitud aastaste esmaste peavalude levimusega.

Peamised tulemused

1. Peavalude epidemioloogilise uuringu küsimustiku koostamine ja testimine (I artikkel)

Koostatud küsimustiku ja diagnostilise algoritmi spetsiifilisus ja sensitiivsus põhiliste diagnostiliste kategooriate suhtes, rakendades Rahvusvahelise Peavalude Klassifikatsiooni kolmanda beetaversiooni kindla peavaludiagnoosi kriteeriume, oli järgmine: kogu migreeni suhtes 0,97 ja 0,56; kogu pingetüüpi peavalu suhtes 0,92 ja 0,52; trigeminaalautonoomsete tsefalalgiate suhtes 1 ja 0,5 ning muude esmaste peavalude suhtes vastavalt 0,98 ja 0,5. Peale võimalike peavaludiagnooside kriteeriumite kaasamist diagnostilisse algoritmi peamiste epidemioloogilistes uuringutes huvipakkuvate kategooriate jaoks küsimustiku ja algoritmi spetsiifilisus märkimisväärselt ei langenud, kuid sensitiivsus suurenes oluliselt. Peale võimalike kriteeriumite kaasamist oli küsimustiku ja algoritmi sensitiivsus migreenile 0,8 ning pingetüüpi peavalule 0,6 ning spetsiifilisus migreenile 0,9 ja pingetüüpi peavalule 0,92.

2. Esmaste peavalude aastane levimus 20–64-aastastel täiskasvanutel Eestis (II artikkel)

3000-liikmelisest valimist saadi kontakti 2162 uuritavaga, kellest omakorda 1215 (56%) vastasid peavaluküsimustikule. Neist 502 (41%) kirjeldasid peavalu esinemist eelneva aasta jooksul. Vanusele, soole, haridustasemele, perekonna-

seisule ja elukohale kaalutud üheaastased levimused olid esmaste peavalude osas järgmised: kogu peavalu 41,0%, kogu migreen 17,7%, kogu pingetüüpi peavalu 18,0%, trigeminaalautonoomsed tsefalalgiad 0,4%, muud esmased peavalud 2,5% ja krooniline igapäevane peavalu 2,7%.

3. Veebipõhise lahenduse rakendatavus esmaste peavalude epidemioloogilises uurimistöös (III artikkel)

Veebipõhist küsimustikku täideti 5347 uuritava poolt 5708 korda. Uuritavatest 3896-l (72,9%) eelnenud aasta jooksul peavalu ei esinenud, 1346-l uuritaval esines üht tüüpi peavalu ning 15 (0,3%) uuritavat kirjeldasid enam kui ühte tüüpi peavalu. Uuringu valimi demograafilised näitajad erinesid statistiliselt oluliselt Eesti 20–64-aastasest populatsioonist, seetõttu kaaluti uuringu valimit vastavalt eale, soole, haridustasemele, perekonnaseisule ning elukohale (maal või linnas). Peavalu all kannatavate uuritavate proportsioon (23,1%) oli veebipõhise uuringu valimis väiksem võrreldes populatsioonipõhises uuringus leituga (41,0%). Samas erinevate kaalutud peavaludiagnooside proportsioonid peavaluga uuritavate seas olid mõlemas uuringus valdavas osas sarnased – krooniline migreen 2% ja 2%, krooniline pingetüüpi peavalu 4% ja 4%, trigeminaalautonoomsed tsefalalgiad 1% ja 1%, muud esmased peavalud 6% ja 5% ning teadmata peavalud 5% ja 3% vastavalt populatsioonipõhise ja veebipõhise uuringu peavalu kaalutud diagnoosidest. Erinevus esines ainult episoodilise migreeni osas, mida oli veebipõhises uuringus vähem (31% versus 42%), ning episoodilise pingetüüpi peavalu osas, mida oli veebipõhises uuringus rohkem (54% versus 41%) kui populatsioonipõhise uuringu peavaludiagnooside osas.

Järeldused

1. Uurimustöö käigus koostatud ja testitud peavaluküsimustikul oli rahuldava väärtusega spetsiifilisus ja sensitiivsus migreeni ning pingetüüpi peavalu diagnooside osas, kasutamaks küsimustikku edasises primaarsete peavalude epidemioloogilises uurimistöös. Uuringu käigus kinnitus, et peavalude epidemioloogia alastes küsimustikes peaks peavalude diagnoosimisel rakendama nii Rahvusvahelise Peavalude Klassifikatsiooni kindla kui ka võimaliku diagnoosi kriteeriume, kuna nõnda suureneb küsimustiku sensitiivsus ning ei teki peavalude levimuse alahindamist.

2. Uurimustöös leitud esmaste peavalude aastased levimused 20–64-aastaste täiskasvanute seas Eestis on sarnased varasemalt avaldatud levimuse näitajatega teistes Euroopa riikides, välja arvatud episoodilise pingetüüpi peavalu osas. Episoodilise pingetüüpi peavalu madal levimus antud uuringus on suure tõenäosusega alahinnatud. Uurimuse tulemused viitavad, et nagu ka teistes Euroopa riikides, on esmased peavalud Eestiski oluliseks haigestumise, elukvaliteedi languse ning ühiskondlik-majandusliku koormuse põhjuseks.

3. Uurimuse tulemused näitavad, et veebipõhine peavalualane epidemioloogiline teadustöö tuleb arvesse kui potentsiaalne aja- ja ressursisäästlik meetod nendes riikides, mis on infotehnoloogiliselt kõrgesti arenenud ning kus interneti ja veebipõhiste rakenduste kasutamine on üldpopulatsioonis laialt levinud. Selline lähenemine võimaldab koguda suuri uuringuvalimeid suhteliselt lühikese aja jooksul. Lisaks pakuvad infotehnoloogilised lahendused uuritavate identifitseerimismeetodeid, mis väldivad andmete kontaminatsiooni, ning tööriistu digitaalsete küsimustike näol, mis suudavad erinevaid peavaludiagnoose rahuldavalt eristada. Möödapääsmatu on edasine uurimistöö veebipõhise metoodika edasiarendamiseks, leidmaks usaldusväärseid valimi moodustamise ning uuritavate värbamise viise, et saavutada esinduslikke valimeid ning vältida kallutatust ning kõige tõenäolisemalt peavalude levimuse alahindamist veebipõhises epidemioloogilises uurimustöös.

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11. APPENDICES

Appendix A. PRILEVEL headache questionnaire in Estonian.

Küsimustik
Baasandmed
- Vanus
- Sugu
- Pikkus
- Kehakaal
- Haridus
- Elan
  - maal
  - linnas
- Perekonnaseis
- Treeningtundide arv nädalas
- Suitsetamine (mitu sigaretti päevas?)
- Viimase aasta jooksul tarbinud kohvi keskmiselt … tassi päevas
- Kui sageli viimase aasta jooksul keskmiselt tarbisite alkohoolseid jooke (õlu, vein, viin jt):
  - Mitte kunagi/väga harva
  - 1–3 korda kuus
  - 1 kord nädalas
  - 2–4 korda nädalas
  - 5–6 korda nädalas
  - igapäevaselt

Ankeet
Kas Teil on viimase aasta jooksul esinenud KORDUVAID peavalusid, mis EI OLNUD tingitud ägedast nakkushaigusest, tarvitatud ravimi(te) kõrvaltoimest, meditsiinilisest protseduurist või toksilis(t)e aine(te)ga kokkupuutumisest (k.a. alkohol ja selle järgne ehk nn. pohmelli peavalu)?
1. Jah
2. Ei

Järgnevalt palume Teil kirjeldada oma tüüpilist peavalu nii täpselt kui võimalik, vastates allolevale 14 küsimusele ja nende alaküsimustele. Kui Teil esineb mitut erinevat tüüpi peavalusid, siis palun täitke iga peavalu tüübi kohta sama küsimustik eraldi.
1. Peavalu lokalisatsioon
   a. Otsmik
   b. Meelekoht
   c. Pealagi
   d. Kukal
   e. Kael
   f. Nägu
   g. Silm, selle ümber ja taga
   h. Kogu pea
   i. Juustega kaetud kuni 6 cm suurune muutumatu ala

2. Peavalu poolsus
    a. Peavalu esineb mõlemal peapoolel korraga
    b. Peavalu asub ühel peapoolel
        i. Ainult paremal
        ii. Ainult vasakul
        iii. Vaheldumisi kas paremal või vasakul
3. Valu iseloom
    a. Suruv, pressiv, pigistav, tuim
    b. Tuikav, pulseeriv
    c. Lõikav, torkiv
    d. Sähviv, elektrilöögitaoline
4. Valu tugevus 0–10 palli süsteemis, kus 0 on valu puudumine, 10 on kõige tugevam võimalik valu üldse
5. Kas valule **eelnevad** (kuni 1 tund enne valu algust) või **koheselt koos valu algusega** (kestvusega kuni 1 tund) tekivad muud sümptomid/kaebused?
    a. Ei
    b. Jah:
        i. nägemishäired (v.a. topeltnägemine)
        ii. naha tundlikkuse häired (tuimus, „sipelgate jooksmine“, „nõelte torkimine“ jms)
        iii. kõnetakistus
        iv. ühe kehapoole nõrkus
        v. pudistav kõne
        vi. pearinglus
        vii. kohin/vilin/undamine kõrvades
        viii. kuulmislangus
        ix. topeltnägemine
        x. koordinatsioonihäired
        xi. teadvushäire
        xii. üldine nõrkus, väsimus
        xiii. uimasus
        xiv. mäluhäired
        xv. meeleoluhäired
6. Kas valuga **kaasuvad** muud sümptomid/kaebused?
    a. Ei
    b. Jah
        i. Iiveldus
        ii. Oksendamine
        iii. Valguse talumatus
        iv. Müra talumatus
        v. Lõhnade talumatus
        vi. Tavapäraste igapäevaste füüsiliste tegevuste talumatus või nende vältimine
        vii. Rahutus, erutus, püsimatus
        viii. Valuga sama peapoole:
            - silma punetus ja/või pisaravool
            - ninakinnisus ja/või vedel eritis
            - silmalau turse
            - otsmikupiirkonna/näo higistamine
            - otsmikupiirkonna/näo punetus

- „lukus“ tunne kõrvas
- pupilli kitsenemine ja/või silmalau allavaje

ix. Valuga samapoolne näotuimus

7. Ühe valuhoo tavaline kestvus (juhul, kui ei tarvitata valuvaigisteid või valu nendele ei allu) on … sek/min/h/päeva kuni … sek/min/h/päeva.
8. Peavalu hoogude keskmine sagedus on … hoogu päevas/kuus/aastas.
   a. Peavalu oli esimesest päevast igapäevane ja pidev, pole olnud valuvabu perioode
      i. Jah
      ii. Ei, aga peavalu esineb rohkem kui 1 päeval kuus
      iii. Ei, aga peavalu esineb harvem kui 1 päeval kuus
      iv. Peavaluga päevade arv kuus on ...
   b. Kui peavalud esinevad järjestikuste hoogude ehk „kobaratena“, siis need perioodid kestavad keskmiselt … päeva/nädalat ning nende perioodide valuvaba vahe on
      i. Lühem kui 1 kuu
      ii. Pikem kui 1 kuu
   c. Kas indometatsiini kasutamine **täielikult** ennetab hoogusid?
      i. Jah
      ii. Ei
      iii. Ei ole indometatsiini tarvitanud
9. Kas peavaluhood on **ALATI ja AINULT** seotud kindla tegevusega?
   a. Ei
   b. Jah:
      i. Köha
      ii. Füüsiline pingutus või vahetult peale seda
      iii. Seksuaalne aktiivsus (peavalu süveneb koos seksuaalse erutusega ja/või tekib järsku vahetult enne või orgasmi ajal)
      iv. Külma joogi/söögi tarbimine ja/või peapiirkonna kokkupuude külmaga
      v. Lennukiga reisimise ajal. Valu tekib:
         - lennuki õhku tõusmisel
         - lennuki maandumisel
         - lendamisel saavutatud stabiilsel lennukõrgusel
      vi. Uni
10. Kas Teie peavalusid võivad esile kutsuda mingisugused välistegurid?
    a. Ei
    b. Jah
       i. Teatud toidud või joogid (v.a. alkohol)
       ii. Alkohoolsed joogid
       iii. Toitumiskordade vahelejäämine, nälg
       iv. Vedelikupuudus, janu
       v. Vaimne pinge/stress
       vi. Füüsiline pingutus/stress
       vii. Sundasendid
       viii. Arvutimonitori ja/või teleekraani jälgimine
       ix. Unerežiimi muutused
       x. Ilmastiku muutused
       xi. Menstruatsioon
       xii. Näo teatud punktide katsumine, nendele vajutamine
       xiii. Hammaste pesemine
       xiv. Toidu mälumine

xv. Reisimine kõrgmäestiku piirkondades
xvi. Muu

11. Peavalu hoogude tekkimisel olen viimase 3 kuu jooksul tarvitanud selle vastu valuvaigisteid:
    a. Ei tarvita
    b. Jah, tarvitan harvemini kui 1 päeval kuus
    c. Jah, tarvitan sagedamini kui 1 päeval kuus

    Valige rippmenüüst Teie poolt tarvitatav(ad) ravim(id).
    - Mitmel päeval kuus Te tarvitate mitut erinevat valuvaigistit samal päeval?

12. Peavalud esinevad mul alates … eluaastast.
13. Kas Teil on kunagi esinenud peatraumat?
    a. Ei
    b. Jah
        i. Peavalu tekkis … tundi/päeva/kuud/aastat peale vigastust
        ii. Peavalu esines juba enne peatraumat
14. Kas te olete oma peavalude tõttu pöördunud
    a. perearstile
    b. neuroloogile
    c. alternatiivmeditsiini esindaja poole

- Luban minu peavalude põhjuste täpsemaks selgitamiseks võtta minuga ühendust peavalu arstidel. Olen teadlik, et sellisel juhul muutuvad minu isikuandmed arstile nähtavateks.
- E-maili teel: ……@.....
- Telefoni teel: ……

12. PUBLICATIONS

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Estonian Movement Disorders Society – member

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Toom K, Laud T, Braschinsky M. One questionnaire to diagnose most of the primary headaches: the PRILEVEL pilot study. Cephalalgia 2015; 35(65): 154–155.

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	Rahvusvaheline Peavalu Selts – liige
	Euroopa Neuroloogiaakadeemia – liige
	Eesti Arstide Liit – liige
	Eesti Liigutushäirete Selts – liige

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