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An opportunity for patient-centered care: Results from a secondary analysis of sex- and gender-based data in mobile health trials for chronic medical conditions

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ABSTRACT

Traditional medical practice has suffered from male bias, which can lead to sub-optimal treatment options for female patients and increase the incidence of severe side-effects in this population. Mobile health applications, mHealth apps, represent one essential component of the shift towards consumer-centered self-administered individualized health. To prevent sex-specific bias it is important that trials consider sex and gender when developing mHealth apps. We evaluated the inclusion and reporting of sex and gender at all levels in mHealth randomized controlled trials (RCTs). To this end, we conducted a secondary analysis of a large study database addressing the effectiveness of app interventions on clinical outcomes in patients with chronic medical conditions. We followed the 5 steps described in the framework by Arksey and O'Malley and the guidelines of the PRISMA-ScR. Of the 72 app-based RCTs which reported information about sex overall, 62 included individuals of both sexes. The concept of gender was not addressed in any of the studies. The consideration of sex aspects in the design, execution and reporting of mHealth RCTs was minimal or absent. To adequately address the health and preventative needs of the mHealth user population, sex and gender should be systematically included in the research, development and evaluation of mHealth applications.

1. Introduction

Traditional medical practice has suffered from a male bias that can lead to sub-optimal treatment options and a higher incidence of, potentially deadly, side-effects in the female patient population [1,2]. The reporting of sex and gender-related data is increasing in the medical literature over time, but substantial variations still exist between disciplines. [3]. Nevertheless, sex and gender are increasingly recognized as health modulators in the (bio)medical field. The impact of sex and gender on the development, diagnosis, treatment and long-term effects of diseases is now well documented [4,5]. Since funding agencies are calling for sex/gender-sensitive research [6,7] and scientific journals are applying more stringent criteria to its reporting [8,9], researchers are prompted to engage with the subject more thoroughly.

Abbreviations: App, application (software); BP, blood pressure; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HbA1c, Hemoglobin A1C; ICD-10, International Classification of Diseases 10th Revision; ICU, intensive care unit; mHealth, mobile health; PDA, personal digital assistant; PRISMA-ScR, Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews; PTSD, Post-traumatic stress disorder; RCT, randomized controlled trial; SUS, system usability score

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Health data is increasingly collected via smartphones and portable devices (so-called wearables) and can be shared with physicians and other health service providers [10]. Mobile health applications, mHealth apps, represent one essential component of the shift towards consumer-centered self-administered individualized health. Digital interventions could provide low entry barriers [11]. This is of special importance for patients with conditions that can be associated with shame, such as mental illnesses, reproductive issues, or cancer.

Sex and gender differences in digital literacy [12], use [13,14] and preferences [15] of mHealth apps, as well as online health information seeking [16,17] have been previously reported. Overall, women tend to report more eHealth and mHealth usage compared to men, but this seemed to be limited to high-income countries [18]. Regardless of these reports, gender-sensitive design is rarely applied in developing mHealth applications and generally limited to female-specific topics [19], such as menstruation, fertility and reproduction. The neglect of sex-specificity upon content development, as well as a lack of gender-sensitivity upon product design might represent significant risk factors for the safety, applicability and market value of the final product. For instance, when apps employ historical clinical data, which underrepresents women, they might perpetuate sex-biased medicine if they use undifferentiated algorithms to mine this data. This might reproduce, e.g. the under-diagnosis of coronary heart disease in women [20]. Gender, on the other hand, might impact the type of product chosen and the access to it. Gender differences in economic means might make some services unavailable for women, especially in low-income countries [21], and overly stereotypical designs for women, i.e. “pink it and shrink it” might dissuade significant consumer fractions. Given these potential risks, the inclusion of sex and gender aspects in the development and execution of trials in the field of digital health appears of importance.

To our knowledge, no previous study has investigated the inclusion of sex and gender aspects in app-based RCTs or mHealth trials. The present study builds upon a previously developed meta-analysis database, assembled by the present authors, on the efficacy and effectiveness of randomized controlled trials for smartphone app-based interventions for chronic medical conditions (PROSPERO registration: CRD42019120119) [22]. The analysis of sex and gender did not fall within the scope of the original meta-analysis concept, but the rigorously selected literature provided the ideal data basis for a focused secondary analysis.

To provide a descriptive overview of sex and gender-related aspects, the following research questions have been formulated: Do women or men participate more often in smartphone app-based RCTs for chronic medical conditions? Is sex or gender considered during sample size calculation in app-based studies for chronic medical conditions? Do app-based RCTs for chronic medical conditions present sex or gender-based outcome data and sex or gender-based user behavior data (adherence, satisfaction and usage data)?

2. Methods

Based on our meta-analysis database [22], we performed a secondary analysis of data following the 5 steps described in the scoping review framework by Arksey and O’Malley and the guidelines of the PRISMA-ScR [23,24]. Data were not quantitatively aggregated, but descriptively summarized [24].

2.1. Data collection

We examined the data extraction work for the meta-analysis of our team by Barth et al. [22]. For preparation of the meta-analysis database, a first literature search was done in October 2016 and an update of the search was conducted in March 2019. No publication period or language limiters were used. Databases searched were PubMed, Web of Science, PsycINFO and CINAHL.

The following search terms were used: smartphone and its synonymous words (“mobile phone”, smart-phone, cellphone, cell-phone, “Smartphone”[MeSH], “Cell Phones”[MeSH]), “Mobile Applications”[MeSH],” mobile app”, Intervention [tiab], treatment [tiab], therap, RCT [tiab], trial [tiab], random [tiab], control [tiab], “Randomized Controlled Stud”, “Clinical Stud”, “clinical trial”, “Random Allocation”, “Treatment Outcome”.

Detailed methods of our meta-analysis can be found in the PROSPERO registration database [22]. For the secondary analysis, sex and gender-related data were extracted, categorized and summarized from the included trials.

2.2. Eligibility criteria

To be included in the meta-analysis database, studies had to be smartphone app-based RCTs with an outcome assessment for participants with chronic medical conditions; the app had to be the main trial intervention, minimum of number of participants had to be 30 (two-armed) or 45 (three-armed).

We excluded the following studies: mHealth interventions delivered by apps aiming at health promotion in participants with risk factor/behavior (rather than ICD-10 diagnosed patients); studies investigating apps only as an add-on intervention of a comprehensive face to face intervention; apps created as a diagnostic tool for participants; apps implemented in tablets or PDA or web-based platforms (i.e. Facebook app).

In the secondary analysis investigating sex and gender-specific reporting we included all trials that reported sex or gender-related numbers of study participants. We excluded studies not reporting sex proportion of participants at baseline. Studies conducted for single-sex patients (either women only or men only) were excluded from the secondary analysis, but listed separately for recording purposes.

2.3. Screening process

Three independent researchers (KE, JW, CK) screened titles/abstracts for potential eligibility and full-texts based on inclusion and exclusion criteria. Disagreement were solved by consensus discussion with one senior researcher (JB).

Gender-related data were extracted by one author (JW) using a structured form, the accuracy of data extraction was checked by another author (IG), the identified discrepancies were resolved through consensus discussion between the two raters supported by the senior researchers (DP and SOP).

2.4. Data charting process

2.4.1. Data extraction form

A data-charting form was developed by one of the authors (JW) to determine variables for extraction. Two senior researchers (DP and SOP) checked and verified the form. Another reviewer (IG) tested the form with a small subset of included studies. The following data items were extracted from the studies: author(s), year of publication, country of origin, study population, sample size, gender distribution, factors considered during sample size calculation, gender-related primary outcome data, adherence data, satisfaction data, usage data, gender-related adherence, satisfaction and usage data.

For this study any sex and gender-related primary outcome data was included, without having to be pre-defined as primary outcome variable.

2.4.2. Data items definitions

We focused on the extraction of adherence and satisfaction data of the study app only. We did not include items that focused on adherence and satisfaction to the treatment.

Definitions for data categories of adherence and satisfaction were

iteratively defined during the charting process. Data was categorized as “satisfaction” data when studies described users’ feeling about- or experience with the study app. Data was categorized as “adherence” data when studies reported the amount of time that the study app was used or compliance rates for the study app. Data was categorized as “usage” data when the data aimed at reporting “engagement with app”, “system usability score (SUS)”, "app utilization rate", “total number of clicks”.

2.5. Data summary and synthesis

The concept of sex and gender-related data in app studies were structurally identified and categorized. Study characteristics were reported using table and chart. Gender-related primary outcome and gender-related user pattern (adherence and usage of the study app), as well as satisfaction data were extracted and reported in descriptive statistics.

3. Results

3.1. Study selection and characteristics

The search strategy yielded 10,711 potential manuscripts. After removing duplications (n = 2854) and eliminating by a first pass through the titles and abstracts, 289 potentially relevant studies were included. Screening the full-text and applying eligibility criteria resulted in 72 studies. Of those 72 studies 10 studies were excluded based on the following criteria: one study on Parkinson’s disease [25] did not report mean age and sex proportion of the participants; eight studies [26–33] with 1182 women included only female participants (breast cancer, asthma control in pregnancy, stress urinary incontinence, women with chronic widespread pain, etc.); one study developed for prostate cancer patients [34] included 100 male participants. In the remaining 62 studies recruiting both male and female participants (n = 8736), the percentage of female participants was slightly lower (n = 4006, 46%) than the percentage of male participants (Fig. 1).

The included app-based studies focused on various diseases: 19 out of 62 studies investigated people with diabetes (type 1 or type 2); 14 studies patients with hypertension and cardiovascular disease (CVD) (heart failure, myocardial infarction, coronary heart disease, etc.); 11 studies focused on participants with mental disorder (dispersion, PTSD, schizophrenia, etc.); 4 studies addressed cancer patients; 5 studies were developed for respiratory and pulmonary disease (asthma, allergic rhinitis, COPD); 2 app-based trials investigated Parkinson’s disease; 1 study app was designed for pain; 8 studies were conducted for patients with other medical conditions, including survivors of critical illness (patients from adult medical, cardiac and surgical ICUs), insomnia, chronic hepatitis B, rehabilitation after lumbar spinal surgery, patients with musculoskeletal conditions, colorectal polyps, psoriasis and stoma. An overview of study characteristics is presented in Table 1. Additionally, a quantitative overview of the target disease conditions of the app-based RCTs is presented in Fig. 2. Numbers may overlap because two studies focused on more than one category of disease.

3.2. Terminology

There is an ongoing discussion in the research community about the definition and reporting of sex and gender in health research. In the current study we worked with information from health apps, which employed mostly self-reported data. We do not have access to the wording of the specific questions asking participants to describe their identity. For the purpose of this study we assumed that in most cases a single question asking individuals to identify as female/male was employed. None of the reported studies paid specific attention to the concept of gender and no additional information about its potential analysis was available. Therefore, we chose to refer to all of the data as sex-specific in the further reporting. We acknowledge that gender (identity, norms and relationships) might play a role in the choice and use of these applications, but the included manuscripts did not offer methodological options to assess this in a robust manner.

3.3. Sample size calculation

The mean sample size of the studies was 140.9 (SD = 115.6), with a range from 30 to 626 participants. The sample included 10 trials with larger sample sizes, equal to or exceeding 200 participants. A total of 47 studies reported the sample size calculation methods, none of them explicitly considered sex during sample size calculation. Estimated effect on primary outcome, standard deviation, power, and dropout-rate were the main factors considered during sample size calculation.

3.4. Primary outcome and sex-related data

Among the 62 studies including both male and female participants, 4 (6%) provided sex-related primary outcome data [35–38]. One study addressing type 1 diabetes [35] reported that “greater HbA1c reduction was obtained in… male gender…”. Another study focusing on blood pressure control [36] reported “gender appeared to influence home self-measured BP…”. A study investigating Parkinson’s disease [37] reported, "females… tend to benefit more… (from the study intervention)". A study conducted for diabetes patients against diabetes-related distress and depression [38], reported: “we found no overall effect of the intervention on diabetes distress or depression, nor did we find treatment differences by sex…”.

3.5. Satisfaction, adherence and usage and sex-related data

In total 29 out of 62 studies (47%) reported adherences data of the study app, 2 (3%) trials [37,39] provided sex-specific data. A study aiming at the stimulation of physical activity among COPD patients [39] reported that “dropout… was also higher among females.” Another study (2%) for Parkinson’s patients [37] reported “there was an indication that women were more adherent than men, but this was not statistically significant.” 20 studies (32%) reported overall satisfaction data, however, no sex and gender-related satisfaction data was reported. Altogether, 35 studies (56%) reported usage of the corresponding study app but no sex-disaggregated usage data was reported.

4. Discussion

To the best of our knowledge this secondary analysis of our meta-analysis database provides the first overview of the consideration of sex and gender as a primary variable in RCTs investigating mHealth for chronic medical conditions. We found that the participation rate of women in the app-based RCTs for chronic medical conditions was generally slightly lower than that of men. None of the included studies defined the performance of sex-disaggregated analysis and the provision of sex-disaggregated results as study objectives. Sex was rarely considered during sample collection, and was not considered upon power calculation for the following analysis. Only four studies reported sex-specific considerations related to the primary outcome and only two provided sex-specific data on adherence. Overall, the consideration of sex-specific data in development and reporting of mHealth RCTs for chronic medical conditions is minimal or absent. The concept of gender was not addressed in any of the studies.

Our results indicate a neglect of sex-specific data at different levels. Sex has been ignored as a medically-relevant variable from a content perspective, but it is also being ignored as a primary element for the methodological robustness of clinical trial performance and reporting.

Ignoring sex as a biological variable will affect the reliability and possibly the safety of the product. Sex differences correlate with risk factors [40] and should thus be considered in designing algorithms for disease management and prevention. Sex differences impact symptoms

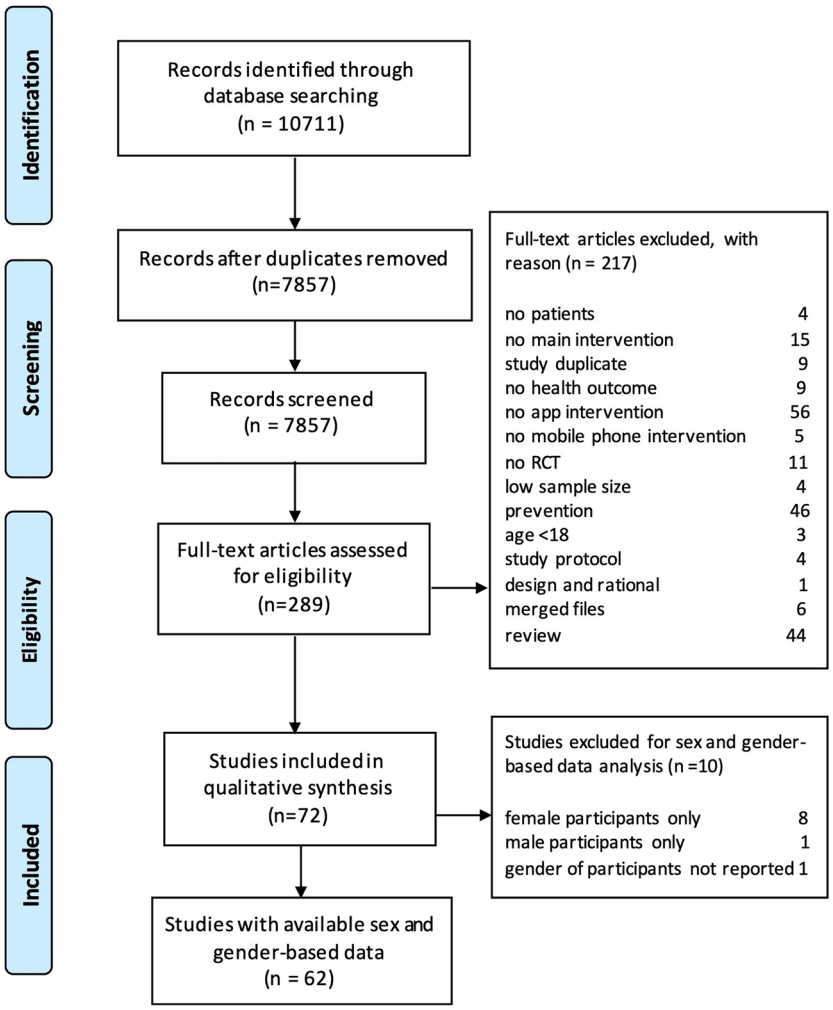


Fig. 1. Flow chart.

of disease, such as in the case of coronary artery disease, asthma and Parkinson´s disease [41]. Also, sex differences correlate with the incidence of pharmacological side effects and need to be considered in the long-term management of chronic diseases. Since diagnostic support and long-term management are some of the main goals of mHealth applications with a clinical focus, neglecting sex aspects in their design will represent a crucial risk.

The current results also point to the disregard of sex as a primary factor for the increase of robustness and reproducibility of clinical trials. RCTs are considered the gold standard for quantitative evaluation in medicine; their methodological standards should be the highest compared to other types of study designs. The included manuscripts did not allow for sex-disaggregated analysis in most cases, since this was not considered upon power calculation. Regardless of the content of the study, RCTs should disaggregate their analyses and reporting by sex to increase transparency, avoid statistical fallacies and facilitate future meta-analyses [42]. Additionally, only 38 (61%) of the studies overall reported a power calculation. The number of included participants was often too low to allow for any stratified analysis. This might not just be problematic for sex-disaggregation, but potentially for all relevant subgroup analyses.

Another interesting finding was that 9 out of the 72 (13%) identified app-based RCTs were conducted for single-sex (either female only or male only) patients. Eight trials were designed only for women, i.e. women with widespread pain, breast cancer, and stress urinary incontinence, one trial was developed for men with prostate cancer. This might point to an increased focus on women´s health in digital interventions and mHealth research.

We performed the first secondary analysis on the inclusion of sex and gender in RCTs investigating mHealth apps for chronic medical conditions. To comprehensively identify all the sex and gender-relevant data, we followed the 5 steps of the scoping review guideline to extract and evaluate data on sex-related inclusion, analysis and patterns of use. This study focuses only on mHealth studies using smartphone applications for chronic medical conditions. This represents a specific subgroup of mHealth applications and results might have been different for eHealth studies, including web-based interventions. Furthermore, we included studies published until March 2019. Given the current dynamic in the research fields of sex and gender-sensitive medicine and digital health, more recent studies might have placed more attention on the subject. It is, however, unlikely that the dynamics completely shifted in the last 12 months.

Overall, we identified a very limited attention for sex and gender in this specific field of mHealth, which can bear several risks for the users. Sex differences can potentially affect prediction accuracy and efficacy of the apps, while gender aspects can influence behavioral change and usage patterns as well as adherence to mHealth application use. To fill the existing knowledge-gap in this area, we encourage researchers in the field of digital health, and especially mHealth, to include sex and gender into their research and practice. Sex and gender should be systematically considered when designing clinical trials. Sample sizes need to be adequately powered to allow for stratified subgroup analyses. Furthermore, sex and gender-disaggregated data needs to be collected, analyzed and reported when performing these trials. We

Table 1
Study characteristics and percentages of female participants (ascending publication year).

Author, year	Country	Target Disease	Participants, N	Female Participants, n (%)
Quinn et al. 2011	USA	diabetes	163	82 (50.3%)
Seto et al. 2012	Canada	hypertension and CVD	100	21 (21%)
Kirwan et al. 2013	Australia	diabetes	72	44 (61.1%)
Orsama et al. 2013	Finland	diabetes	48	22 (45.8%)
Rossi et al. 2013	Italy	diabetes	127	67 (52.8%)
Holmen et al. 2014	Norway	diabetes	151	62 (41.1%)
Mendelson et al. 2014	France	Hypertension and CVD	107	18 (16.8%)
Tabak et al. 2014	Netherlands	respiratory and pulmonary disease	30	11 (36.7%)
Varnfield et al. 2014	Australia	hypertension and CVD	94	12 (12.8%)
Cingi et al. 2015	Turkey	respiratory and pulmonary disease	228	116 (50.9%)
Drion et al. 2015	Netherlands	diabetes	63	23 (36.5%)
Faurholt-Jepsen et al. 2015	Denmark	mental disorder	67	45 (67.2%)
Karhula et al. 2015	Finnland	diabetes; hypertension and CVD	519	202 (38.9%)
Skrøvseth et al. 2015	Norway	diabetes	30	19 (63.3%)
Van der Weegen et al. 2015	Netherlands	respiratory and pulmonary disease; diabetes	199	102 (51.3%)
Arean et al. 2016	USA	mental disorder	626	494 (78.9%)
Johnston et al. 2016	Sweden	hypertension and CVD	166	32 (19.3%)
Jeon et al. 2016	Korea	other	53	5 (9.4%)
Quinn et al. 2016	USA	diabetes	118	59 (50%)
Vorrink et al. 2016	Netherlands	respiratory and pulmonary disease	157	79 (50.3%)
Wang et al. 2016	China	other	203	74 (36.5%)
Baron et al. 2017	UK	diabetes	81	35 (43.2%)
Bender et al. 2017	USA	diabetes	45	28 (62%)
Christoforou et al. 2017	UK	mental disorder	142	118 (83.1%)
Dang et al. 2017	USA	hypertension and CVD	61	22 (36.1%)
Del Rosario et al. 2017	Australia	hypertension and CVD	66	24 (36.4%)
Horsch et al. 2017	Netherlands	other	151	94 (62.3%)
Kerfoot et al. 2017	USA	diabetes	456	28 (6.1%)
Kleinman et al. 2017	India	diabetes	90	27 (30%)
Kuhn et al. 2017	USA	mental disorder	120	83 (69.2%)
Lambert et al. 2017	Australia	other	80	52 (65%)
Lakshminarayana et al. 2017	UK	Parkinson's disease	201	79 (39.3%)
Mantani et al. 2017	Japan	mental disorder	164	87 (53.1%)
Quinn et al. 2017	USA	diabetes	114	56 (49.1%)
Sun et al. 2017	Denmark	cancer patients	46	14 (30.4%)
Widmer et al. 2017	USA	hypertension and CVD	71	13 (18.3%)
Agarwal et al. 2018	Canada	diabetes	223	106 (47.5%)
Ben-Zeev et al. 2018	USA	mental disorder	163	67(41.1%)
Cox et al. 2018	USA	other	80	35 (43.8%)
Di et al. 2018	China	cancer patients	132	49 (37.1%)
Ellis et al. 2018	USA	Parkinson's disease	51	23 (45.1%)
Hur et al. 2018	Korea	mental disorder	34	30 (88.2%)
Krzystanek et al. 2018	Poland	mental disorder	290	116 (40%)
Kwon et al. 2018	Korea	respiratory and pulmonary disease	85	15 (17.6%)
Lakshminarayan et al. 2018	USA	hypertension and CVD	50	14 (28%)
Lüdtke et al. 2018	Germany	mental disorder	88	69 (78.4%)
Mayer et al. 2018	USA	cancer patients	284	147 (51.8%)
Márquez Contreras et al. 2018	Spain	hypertension and CVD	148	77 (52%)
Morawski et al. 2018	USA	hypertension and CVD	411	247 (60%)
Ormel et al. 2018	Netherlands	cancer patients	32	4 (12.5%)
Santo et al. 2018	Australia	hypertension and CVD	163	20 (12.3%)
Sarfo et al. 2018	Ghana	hypertension and CVD	60	21 (35%)
Svendsen et al. 2018	Netherlands	other	134	52 (38.8%)
Choi et al. 2019	Korea	pain	84	57 (67.9%)
Contreras et al. 2019	Spain	hypertension and CVD	148	77 (52%)
Donker et al. 2019	Netherlands	mental disorder	193	129 (66.8%)
Höchsmann et al. 2019	Switzerland	diabetes	36	8 (22.2%)
Hou et al. 2019	China	other	168	90 (53.6%)
Lee et al. 2019	Korea	other	65	26 (40%)
O'Toole et al. 2019	Denmark	mental disorder	129	54 (41.9%)
Sun et al. 2019	China	diabetes	91	54 (59.3%)
Yu et al. 2019	China	diabetes	185	70 (37.8%)
Total			8736	4006(45.86%)
Kristjánsdóttir et al. 2013[a]	Norway	pain	135	135 (100%)
Asklund et al. 2016[a]	Sweden	other	123	123 (100%)
Zairina et al. 2016[a]	Australia	respiratory and pulmonary disease	72	72 (100%)
Mackillop et al. 2018[a]	UK	diabetes	203	203 (100%)
Miremberg et al. 2018[a]	Isreal	diabetes	120	120 (100%)
Kim et al. 2018[a]	Korea	cancer patients	76	76 (100%)
Zhu et al. 2018[a]	China	cancer patients	114	114 (100%)
Park et al. 2019[a]	Korea	cancer patients	339	339 (100%)
Lee et al. 2019[b]	Korea	cancer patients	100	0 (0%)
Ginis et al. 2016	Belgium/Israel	Parkinson's disease	38	NA (NA)

[a] study recruited only female participants.
[b] study recruited only male participants.

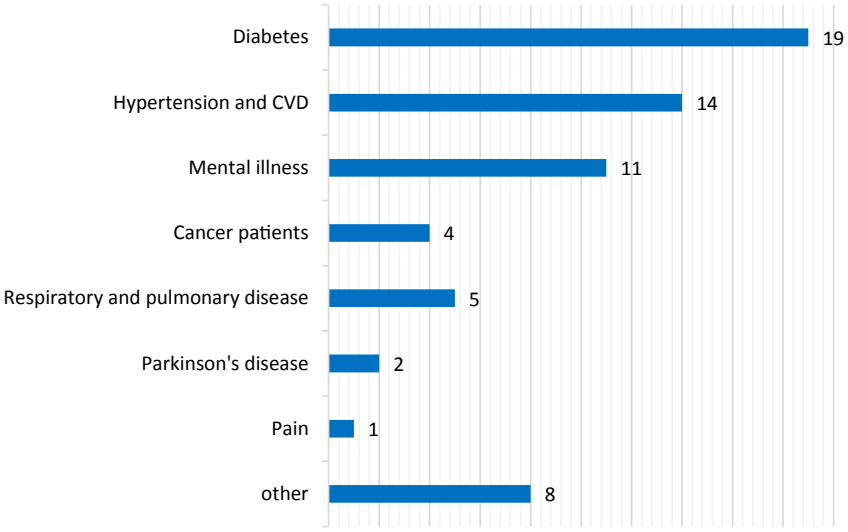


Fig. 2. Target diseases of app-based RCTs.

recommend using existing reporting standards, such as the "Sex and Gender Equity in Research" guidelines (SAGER) [43] or possibly even going further and creating new sex and gender-sensitive standards for digital health research in consideration of the specific practices in the field.

5. Conclusion

Sex and gender are poorly considered and reported in mHealth/app-based studies for chronic medical conditions. To effectively address the specific health and preventative needs of mHealth users, sex and gender should be systematically included in the research, development and evaluation process of mHealth applications.

Contributors

Jiani Wang performed data extraction, analyzed the data, and drafted the manuscript.

Jürgen Barth conceived the research, performed data extraction, and reviewed the manuscript for important intellectual content.

Irene Göttgens analyzed the data, and reviewed the manuscript for important intellectual content.

Karma Emchi performed data extraction, and reviewed the manuscript for important intellectual content.

Daniel Pach conceived the research, supervised data analysis, and drafted the manuscript.

Sabine Oertelt-Prigione conceived the research, supervised data analysis, and drafted the manuscript.

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Ethical approval

The study used secondary data and so ethical approval was not applicable.

Conflict of Interest

The authors declare that they have no conflict of interest.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

Provenance and peer review

This article has undergone peer review.

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