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Gender representation in drug development studies for diabetes mellitus. A systematic review

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ABSTRACT

Background: During the last 20 years, the prevalence of diabetes mellitus (DM) has increased drastically, and so has the number of associated medicine and drug development studies. Despite knowing that men and women respond differently to DM medicines, biological gender differences still tend not to be prioritized during medicine development.
Objective: This study examined gender representation in medicine development studies for DM.
Method: We conducted a systematic review, and in February 2022, we searched EMBASE (Excerpta Medica Database), MEDLINE (Medical Literature Analysis and Retrieval System Online) and PubMed using a block search strategy. Randomized controlled studies (RCTs) including people diagnosed with DM (any type) aged 18–65 years were included. The Consolidated Standards of Reporting Trial 2010 checklist was applied to assess the studies' reported quality. The results are presented in a narrative synthesis.
Results: Nine studies met the inclusion criteria. On average, women represented 31.4% of study participants, and similarly, for each trial phase, women were less represented than men.
Conclusion: This review showed an unequal gender representation in drug development studies for DM, with women and men representing 31.4% and 68.6% of the study participants, respectively, in the included studies. However, gender differences in medical drug studies might be due to specific exclusion criteria, participants' behaviour toward attending in medicine development or the law in the country of origin.

Summary

This paper examines gender representation during the development of medicine for diabetes mellitus (DM) in randomized controlled trials. A systematic review and a narrative synthesis were conducted, including nine studies.

We found that 31.4% of trial participants during medicine development for DM were women, and 68.6% were men. This unequal gender distribution might be due to ethical or political principles or scientific traditions.

1. Introduction

During recent decades, the number of people diagnosed with diabetes mellitus (DM) has increased and was estimated at 537 million people worldwide in 2021 [1]. Consequently, the development and consumption of medicine for progressive chronic diseases such as DM have also grown substantially [2,3]. The prevalence of DM was estimated in 2016 to be higher for men than women (14.6% vs 9.1%) [4].

Due to the increased development of medicine for DM and the rise in DM cases, the number of reported side effects and adverse events has grown, particularly for women [5–9]. This increase might be related to the medicine development process and could lead to women, more often than men, being treated with medicines that are not appropriate for the hormonal-related gender differences [6,10,11]. Because of the so-called 'one-size-fits-all' principle [5], medicines are tested and administered according to a person's weight but do not always consider their biological gender [6,7] despite studies showing that the pharmacodynamics and pharmacokinetics of men and women differ [5,7,12]. For example, the differences between the male testosterone and the female oestrogen are important for the pharmacokinetics and pharmacodynamics of medicine [13,12] as well as glucose tolerance, which on average is 20% higher for men compared to women [6,14]. This variation will impact the medicine development process and, consequently, the developed medicine [15].

Therefore, in 1993, the US National Institute of Health changed its medical laws to accommodate the number of reported side effects,

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ensuring that biological differences are considered during medicine development [16–21]. Despite this change and the fact that approved medicine is developed under controlled conditions, several epidemiological studies based on national and international data registers show that biological gender differences are still not prioritized during drug development [10,13].

Previous research has shown that gender differentiation exists during medicine development for cardiovascular diseases and, specifically, in medicine development phases [7,8,14]. However, gender distribution during the development of medicine for DM, as well as the consequences of any unequal gender distribution, have yet to be sufficiently investigated. To our knowledge, this has not yet been investigated.

Therefore, the aim of this systematic review was to examine gender representation in medicine development studies for DM.

2. Methods

This study was registered in Prospero (308608) and remained unchanged during the review. The findings are reported according to the PRISMA Group (Preferred Reporting Items for Systematic review and Meta-Analysis) guidelines [22,23].

2.1. Eligibility criteria

We included randomized controlled trials (RCTs), with a minimum of one intervention group and one control group, to ensure that the medicine was developed in high-quality environments and met the current medical laws according to medicine development [17,18,20]. Furthermore, the studies should include people diagnosed with DM (any type) aged 18–65 years. The limit of 65 years was chosen to reduce conflicting results from elderly participants with comorbidities [16,24]. If studies included patients both over and under 18 years of age or over and under 65 years of age, the studies were considered for inclusion only if the data were stratified by age.

Moreover, we only included studies written in either English, Danish, Norwegian or Swedish to reduce misleading translations. Finally, only studies with full online access were considered for inclusion.

2.2. Information sources and search strategy

The search was performed online and conducted in February 2022 in EMBASE (Excerpta Medica Database), MEDLINE (Medical Literature Analysis and Retrieval System Online) and PubMed. An information specialist was included in the design of the block search strategy. The search string was structured using the conceptualization model PICo (Population - Intervention - Context) framework in combination with Boolean operators and truncations [25,26].

Medical Subject Headings were identified using Emtree. Grey literature was included from Cochrane.org and PROSPERO.org to discover unpublished journals, texts, articles and any duplicates of ongoing studies [27]. No duplicate ongoing studies were identified.

The search strategy with blocks was customized to the specific databases and their structures. For a complete search string, see Appendix 1.

2.3. Screening and study selection

Findings from the search string were initially transferred to the reference program Endnote (https://endnote.com/) and afterwards to Covidence (www.covidence.org), where duplicates were removed. In Covidence, the studies were independently screened and identified by two authors (AH, BN). The exclusion criteria were wrong study design, wrong study participant group or wrong treatment. Any disagreement concerning the studies' eligibility was resolved through discussion until a consensus was reached. Studies that met the inclusion criteria were retrieved for a full-text screening by one author (AH), and final inclusion was discussed with the second author (BN). None of the reviewing authors were blinded to journal articles, study authors or institutions.

2.4. Data extraction and data items

Prior to data extraction, a customized table was developed. One author (AH) extracted the data, including bibliographic information, study goals, study design and trial phase, inclusion and exclusion criteria, and the participants' age and gender. The data were then discussed with and validated by a second author (BN).

2.5. Quality assessment

The Consolidated Standards of Reporting Trials (CONSORT) checklist was applied to assess the included studies' quality [28]. The included studies were assessed by one author (AH) and discussed and validated by a second author (BN). The CONSORT quality checklist includes 37 items assessing the title and abstract, introduction, method, result, discussion and other information. No studies were excluded due to the quality assessment.

2.6. Data synthesis and interpretation

The data were descriptively summarized, and a narrative synthesis was applied to present the results from the included studies [27,29]. The narrative synthesis, which appears as an iterative process, helped to draw new perspectives and themes related to gender distribution throughout the synthesis [27].

3. Results

3.1. Study selection

A total of 4401 studies were initially identified. After removing duplicates, 4074 studies remained, of which 4054 were excluded based on title or abstract. The remaining 20 studies were retrieved for full-text reading, of which nine studies met the eligibility criteria. Of the 11 excluded studies, nine were excluded due to wrong study design [30–38], one due to wrong aim [39], and one was excluded because it investigated the effect of a mixed meal rather than the development of medicine and was also not an RCT [40] (see Fig. 1).

3.2. Study characteristics

The included studies were published between 2011 and 2021 and originated from China [41], Germany [42], Iran [43] and Japan [44–47], respectively. One study included data from Mexico, Columbia and the USA [48], and lastly, one of the studies included data from 23 countries [49].

The designs of the included studies were a double-blinded placebo-controlled randomized two-way crossover (longitudinal) [42], a randomized controlled triple-blind trial with placebo and intervention group study [43], two randomized double-blinded parallel studies with placebo [46,48], and five studies with a randomized controlled design [41,44,45,47,49], respectively. The number of study participants varied from 14 [41] to 462 [49], of which women represented between 4 (28.6%) and 199 (43%) of the participants and men between 10 (71.4%) and 263 (57%) of the participants. The intervention period of the included studies varied between 2 [46] and 96 [48] weeks. Further details are presented in Table 1.

3.3. Quality assessment

The methodological quality level varied slightly among the included studies because they met between 18 and 36 out of 37 quality criteria according to the CONSORT checklist. However, some of the studies were

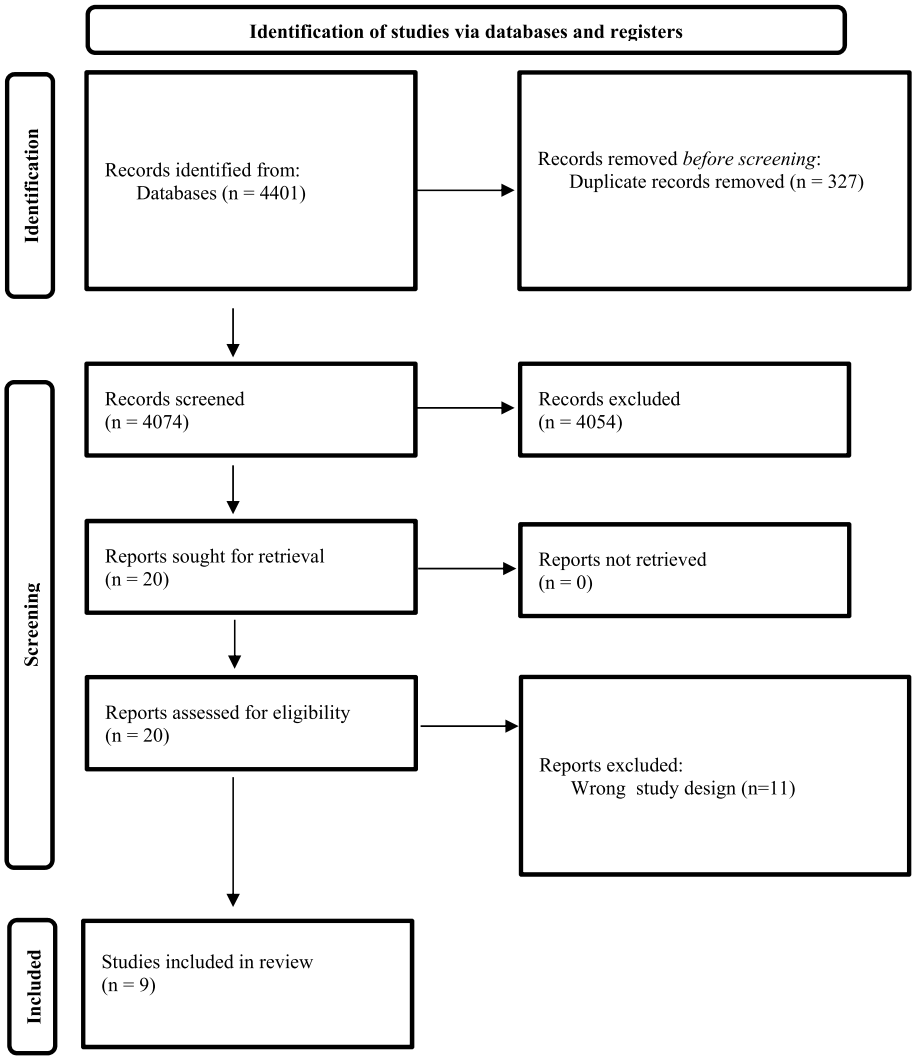

Fig. 1. Flowchart of screening and inclusion process.

assessed to be of lower reporting quality. An example is the study by Hong et al. [42] that met 18 of the 37 criteria because the study was not clearly labelled as an RCT study, and it did not clearly present the eligibility criteria for the study participants. Furthermore, the setting and location for data collection were not presented, and similarly, it was not clarified how the sample size was determined or how the study participants were blinded. Lastly, the study did not present practical information, such as the registration number or name of the trial registry number. By contrast, the study by Dagogo-Jack et al. [49] met 36 of the 37 criteria and lacked only a report of any changes of the results after the trial had begun corroborating item 6b in the CONSORT checklist.

The remaining seven studies meet different criteria with varying numbers of deficiencies from the checklist. The shortcomings included the labelling of the study design as an RCT in the title [42,43,46] or lacking a clear description of the inclusion criteria or reporting of elements in the method [42,45]. In the method section, some of the studies failed to report the number of study participants as well as the randomization process for those participants' recruitment [41–44,48], whereas other studies failed to report how they were completed [42–44, 47].

For further details, see Table 2.

3.4. Narrative synthesis

Gender representation varied among the nine included studies. Women and men represented 14–59% and 41–86%, respectively, of the trial participants. Across the included studies, women represented 31.4% of the trial participants and men the remaining 68.6%.

Furthermore, drug development phases and the number of trial participants varied among the included studies. Thus, we found a more equal gender distribution and a larger number of trial participants in the trial phase III [45,47,49] vs trial phase I-II [41,44,46,48] studies.

Moreover, geography appeared to have some significance because both gender distribution and participant age were more homogeneous in the four studies from Japan compared to the remaining five studies.

Regardless of geography, the gender distribution, average of participants and intervention methods were also quite similar across the included studies.

Even though the gender distribution varied among the studies, we found no direct relation between the nine studies' methods, drug phases and number of trial participants, in relation to the gender distribution.

4. Discussion and conclusion

Based on the included studies, we found women to be underrepresented (31.6% of study participants) compared to men during medicine development for diabetes mellitus (DM). Thus, our result corroborates previous studies showing that women represent 22% of the participants in drug phase I and generally represent 37% of the study participants in drug development studies [16,22,50]. Because the included studies all

Table 1
Characteristics of the included studies.

Author, year and location*	Aim	Study design and data collection method	Participants' characteristics (sex, age)	Intervention method	Conclusion
T. Araki, 2011 (Japan) [46]	Identify whether TAK-875[a] reduced the glucose level for DM2[b] patients	A randomized double-blinded parallel study with placebo phase II	Study participants (n = 65), Men (n = 56), Women (n = 9) Mean age (SD[h]): Placebo, 52.2 (±10.2), TAK-875 100 mg, 52.1 (±8.9), TAK-875 400 mg, 53.4 (±11.3)	The study participants received placebo or TAK-875 for two weeks	TAK-875 had a short-term potential to reduce the glucose level for the study participants with DM2
Dagogo-Jack, 2017 (23 countries) [49]	Whether SGLT2[c] and DPP-4[d] inhibitors can be combined in treatment for DM	A randomized controlled study with a placebo group and two control groups phase III	Study participants (n = 462), Men (n = 263), Women (n = 199) Mean age 59.1 (9.0)	For 52 weeks, the study participants received either placebo, Ertugliflozin and Metformin or Sitagliptin and Ertugliflozin	A combination of Ertugliflozen and Metformin or Sitagliptin and Ertugliflozin reduced the glucose levels
Halvorsen, 2019 (USA, Mexico, Colombia) [48]	Discover the potential of Bexagliflozin as monotherapy for DM[e]	A double-blinded randomized parallel study phase II	Study participants (n = 288), Men (n = 167), Women (n = 116) Mean age (SD): 55.6 (10.6)	For 96 weeks, the study participants received either placebo or Bexagliflozin	After 96 weeks with Bexagliflozin, the glucose level was reduced
Hong, 2013 (Germany) [42]	Examine glucose and insulin concentrations in a meal tolerance test and hyperglycaemic clamp	A double-blinded placebo-controlled randomized two-way crossover (longitudinal) phase I	Study participants (n = 20), Men (n = 16), Women (n = 4) Mean age: 53.7	For four weeks, the study participants received placebo or Palosuran. After the washing-out period, they received an alternative treatment for four weeks	Palosuran did not have glucose-lowering potential or clinical relevance
Inagaki, 2014 (Japan) [44]	Test the effect of the DPP-4 inhibitor SYR-472[f] in DM2 patients	A randomized double-blind placebo-controlled study phase II	Study participants (n = 322), Men (n = 194), Women (n = 128) Mean age (SD): Placebo 61.6 (9.79), SYR-472 12.5 mg: 60.6 (10.24), 25 mg: 58.5 (10.49), 50 mg: 61 (10.18), 100 mg: 57.8 (10.38), 200 mg: 60.5 (11.26).	For 12 weeks, the study participants received placebo or medicine with SYR-472	SYR-472 controlled the glucose level for the study participants with DM2
Inagaki, 2015 (Japan) [45]	To compare a weekly treatment with Trelagliptin or a daily treatment with Alogliptin	A randomized double-blind active-controlled parallel placebo study phase III	Study participants (n = 243), Men (n = 185), Women (n = 58) Median age 62 (54–67)	For 24 weeks, the study participants received 100 mg Trelagliptin weekly, 25 mg Alogliptin daily or placebo	Trelagliptin had the same effect on glucose level as Alogliptin
Kaku, 2015 (Japan) [47]	Examine the effect of Fasiglifam in DM2 patients with an uncontrolled diet and poor exercise habits	A randomized double-blind placebo-controlled study phase III	Study participants (n = 192), Men (n = 136), Women (n = 56) Mean age: 60.4	For 24 weeks, the study participants received placebo or Fasiglifam	Fasiglifam had a clinical effect for the study participants with low risk of hyperglycaemia
Momeni, 2021 (Iran) [43]	Examine the effect of extract from black mulberry leaves on HbA1c %[g]	A randomized controlled triple-blind trial with placebo and intervention group study phase II-III	Study participants (n = 100), Men (n = 75), Women (n = 25) Mean age (SD): 54.79 (±9.20)	For three months, the intervention group received extract from mulberry leaves, whereas the placebo group received water three times a day	The mulberry leaf extract reduced the study participants' fasting glucose level
Wu, 2021 (China) [41]	Examine whether Fotagliptin could act as a DPP-4 inhibitor	A randomized double-blind placebo-controlled study phase I	Study participants (n = 14), Men (n = 10), Women (n = 4) Mean age (SD): Fotagliptin group: 48.3 (7.0), placebo group: 42.0 (6.7)	For 14 days, the study participants received Fotagliptin or placebo treatment	Fotagliptin increased DPP-4 inhibition and had glucose-lowering potential

Abbreviations in Table 1.
[a] TAK-875 = Fasiglifam.
[b] DM2 = Type 2 diabetes mellitus.
[c] SGLT2 = Selektive Sodium Glucose Co Transporter.
[d] DPP-4 = Dipeptidyl-peptidase 4.
[e] DM = Diabetes mellitus.
[f] SYR-472 = Trelagliptin.
[g] HbA1c = glycated haemoglobin.
[h] SD = Standard deviation.

report as having been approved by pharmaceutical laws and ethics committees, the unequal gender representation cannot be explained by the exclusion of women per protocol.

It is possible though that women are excluded because of ethical and legal conditions, physiological and biological differences, or based on financial explanations [9,17,51]. The inclusion of, for example, pregnant or breastfeeding women or women not using prevention can be a challenge for medicine development investors because the inclusion of these women can presuppose a deceleration of other research and further education in both sexes [17,51]. Furthermore, the fact that women's metabolisms change during their hormonal cycle may mean that the pharmaceutical industry should allocate more time and economic resources to accommodate the changes [9]. However, this unequal gender representation might also be due to other elements, such as research traditions, science cultures and the context, as well as the medical companies' economic incentives, as reported in studies investigating the reasons for unequal gender representation in drug studies [11,15,52,53,54,55]. Gender-specific exclusion criteria were found in seven of the included studies, in which women were excluded if they were pregnant, breastfeeding or did not use prevention [15,21,22,52]. This is a way in which medical companies can reduce costs because female biology can be complex to handle during drug development [17, 53]. The biology of women is more complex; their oestrogen and progesterone levels vary during their monthly cycles, influencing the effect of the medicine during the trial period [15]. However, if women are excluded *because* of their sex, studies show that 42% of all women aged between 18 and 49 years would be excluded from drug development studies [56].

Table 2
Quality assessment of the included studies.

CONSORT guideline for reporting RCT studies/item	T. Araki, 2011 (Japan) [46]	Dagogo-Jack 2017 (23 countries) [49]	Halvorsen, 2019 (Columbia, Mexico, USA) [48]	Hong, 2013 (Germany) [42]	Inagaki, 2014 (Japan) [44]	Inagaki, 2015 (Japan) [45]	Kaku, 2015 (Japan) [47]	Momeni, 2021 (Iran) [43]	Wu, 2021 (China) [41]
1a	*No*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*No*	*Yes*
1.b	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
2a + 2b	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
3a	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
3b	*No*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*Yes*
4a	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
4b	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*No*	*Yes*	*Yes*	*Yes*
5	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
6a	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
6b	*Yes*	*No*	*Yes*	*No*	*No*	*No*	*No*	*No*	*Yes*
7a	*Yes*	*Yes*	*No*	*No*	*No*	*Yes*	*Yes*	*No*	*No*
7b	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*No*	*No*
8a	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*	*No*
8b	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*
9	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*	*No*
10	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*	*No*
11a	*No*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*No*	*No*	*No*
11b	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Yes*	*No*
12a +12b	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
13a	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
13b	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
14a	*No*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*No*	*Yes*
14b	*Yes*	*Yes*	*Yes*	*No*	*No*	*Yes*	*No*	*No*	*Yes*
15	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
16	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
17a	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
17b	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
18	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
19	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
20	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
21	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
22	*Yes*	*Yes*	*Yes*	No	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
23	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
24	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
25	*Yes*	*Yes*	*Yes*	No	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
Score	33/37	36/37	36/37	18/37	33/37	35/37	31/37	25/37	29/37

The research of Inagaki et al. [45] differed from the other Japanese studies because no gender-specific exclusion criteria were presented [44–47]. It is worth mentioning that Inagaki and colleagues' study [45] received a high score in the quality assessment and was furthermore approved by the Declaration of Helsinki, the International Council for the Harmonization of Technical Requirements for Human Medicinal Products and Japan's Group for Pharmaceuticals and Medical Devices and the Ministry of Health, Labor and Welfare.

Nevertheless, the consequence of this unequal gender representation during drug development is that medicines not fitting the diversity of the female body are developed. Women can, therefore, more often than men, expect side effects of different levels from the use of medicine. Furthermore, women will overall not experience the anticipated effect of the medicine, and the safety of using the medicine will be lower for women than for men [9–11,12,15,16]. Finally, we have to acknowledge that the prevalence of DM2 is approximately 60% higher in men compared to women [57]. We do, however, still believe that the gender representation in drug development studies is inappropriate.

4.1. Limitations

We consider the relatively low number of final included studies a limitation of our systematic review. We did, however, develop the search strategy in collaboration with an information specialist and believe that the limited number of studies reflect an exhaustive search and rigorous inclusion criteria. Furthermore, the origin of the included studies could be considered a limitation because the research context and research traditions for the study participants from Japan, Germany, Colombia and Iran are not particularly comparable.

4.2. Conclusion and practice implications

This review showed an unequal gender representation in drug development studies for DM, with women and men representing 31.4% and 68.6% of the study participants, respectively, in the included studies.

We believe that this study is of relevance for clinicians as it raises the awareness of gender inequality in drug development studies. However, this paper also emphasizes a need for further research to identify the causes of this unequal gender distribution and investigate whether the phenomenon is widespread.

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Ethics approval and consent to participate

N/a

Consent for publication

N/a

Availability of data and material

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Authors' contributions (CRediT roles)

Conceptualization: AH, BN
Data curation: AH, BN
Formal analysis: AH
Funding acquisition: n/a
Investigation: AH
Methodology: AH, BN
Project administration: AH
Resources: AH
Software: AH
Supervision: BN
Validation: BN
Visualization: AH
Roles/Writing – original draft: AH, BN
Writing – review & editing: BN

Declaration of competing interest

Both authors declare to have no conflicts of interest

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None

Appendix 1. Search string

Population	Intervention	Context
"Diabetes Mellitus"	"Insulin therapy"	"Medicine development"
		EBM
Diabetic*	"Insulin treatment"	"Evidence based medicine"
"Diabetes Mellitus type 2"	"Glycemic control"	"Evidence based cure"
T2D*	Insulin*	"Evidence based treatment"
"Diabetes Mellitus patients"	"Medical care"	"Drug development"
"Insulin dependent patient"	Medicine*	"Pharmaceutical treatment"
	Treatment*	"Pharmaceutical development"

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Further reading

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