

## Review Article

# Effects of diabetes mellitus on semen quality in adult men: a systematic review and meta-analysis

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**Abstract:** Objective: To explore the effects of diabetes mellitus (DM) on semen parameters. Methods: The PubMed, Embase and Cochrane Library databases were searched to identify eligible studies for this meta-analysis. The most recent search was performed in December 2015. Standard mean differences (SMDs) with 95% confidence intervals (CIs) were used to evaluate the effects of DM on semen parameters. Heterogeneity among studies was examined using the Chi-square distribution based on the Q-test and  $I^2$ . When  $I^2 \leq 50\%$  for the Q-test, a lack of heterogeneity among the studies was indicated, and the summary estimate of each study was calculated using the fixed-effects model. Otherwise, the random-effects model was used. Results: A total of 21 independent studies (1218 cases and 1171 controls) were analysed. The results suggested that semen volume, sperm concentration, total sperm motility, progressive sperm motility and normal sperm morphology were significantly lower in DM patients than in nondiabetic controls, and the pooled SMDs (95% CIs) were -0.59 [-0.97, -0.21], -0.52 [-0.94, -0.09], -1.93 [-2.79, -1.08], -3.54 [-5.25, -1.83], and -1.08 [-1.53, -0.62], respectively,  $P < 0.05$ . In addition, sperm DNA fragmentation was significantly higher in DM patients than in nondiabetic controls, and the pooled SMD (95% CI) was 1.99 [0.41, 3.56],  $P < 0.05$ . However, rapid progressive sperm motility and total sperm count in DM patients were not significantly different from those in nondiabetic controls (SMDs (95% CIs) -0.85 [-1.95, 0.24], and -0.23 [-0.71, 0.25], respectively,  $P > 0.05$ ). Conclusion: Our study indicated that DM had negative effects on semen quality.

**Keywords:** Diabetes mellitus (DM), semen parameters, systematic review, meta-analysis

## Introduction

Diabetes mellitus (DM) is one of the most prominent current public health threats due to its long-term complications and rising incidence [1]. According to the latest study from the International Diabetes Federation in 2013, 382 million people were suffered from DM worldwide, and the prevalence of DM is expected to be 592 million by 2035 [2].

DM is a complicated chronic metabolic disorder characterised by hyperglycaemia, which often results from defects in insulin secretion, insulin action, or both [3]. Most patients with DM are diagnosed during their reproductive age [4], and it is expected that male fertility problems associated with DM will dramatically rise in the near future. Growing evidence suggests that

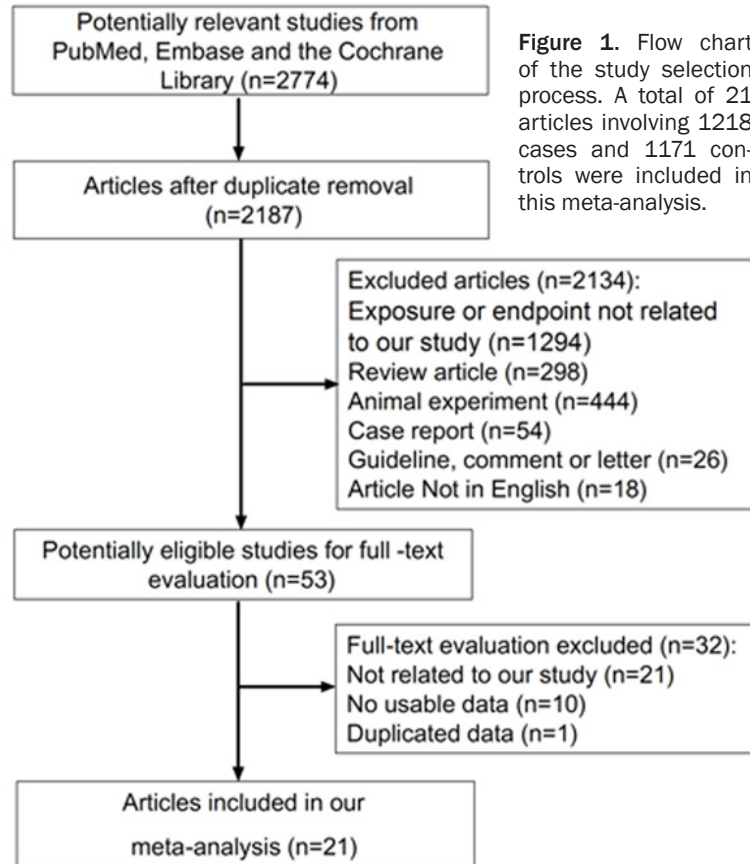
DM may adversely affect male reproductive function on multiple levels [5]. Several studies have evaluated the effects of DM on sperm parameters, but the subject has not been systematically evaluated. Studies of the effects of DM on sperm parameters have reported inconsistent results; some studies showed significant alterations in semen parameters due to DM, while others did not [4, 6-10]. Thus, to assess the effects of DM on basic semen parameters, we conducted this meta-analysis.

## Materials and methods

### Search strategy

The PubMed, Embase and Cochrane Library databases were searched to identify eligible studies reporting the effects of DM on basic

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**Figure 1.** Flow chart of the study selection process. A total of 21 articles involving 1218 cases and 1171 controls were included in this meta-analysis.

cluding studies included the following: (1) the article was a review, case report, comment, guideline or letter; (2) the article reported animal research; (3) there were no control cases; (4) no usable data were reported. In addition, only studies published in English were included in our study.

### *Data extraction and quality assessment*

The following data were extracted: the last name of the first author, the year of publication, the country, the numbers and mean age of participants, the study design, the DM classification, the abstinence time and data related to the outcome of semen volume, sperm concentration, total sperm motility, progressive sperm motility, rapid progressive sperm motility, normal sperm morphology, total

sperm count, and sperm DNA fragmentation. All data were independently extracted by two investigators (JZ and XD) according to the prespecified selection criteria. Controversial issues were resolved through further discussion. In the meta-analysis, we completed the quality assessment according to the primary criteria for nonrandomised and observational studies of the Newcastle-Ottawa Scale (NOS) for assessing quality.

### *Statistical analysis*

Standard mean differences (SMDs) with 95% confidence intervals (CIs) were used to evaluate the effects of DM on semen parameters. Heterogeneity among studies was examined using the Chi-square distribution based on the Q-test and  $I^2$ . When  $I^2 \leq 50\%$  for the Q-test, a lack of heterogeneity among studies was indicated, and the summary estimate of each study was calculated using the fixed-effects model. Otherwise, the random-effects model was used. A sensitivity analysis was performed to evaluate the influence of a single study on the

semen parameters. The most recent search was performed in December, 2015. The results were limited to articles published in English. The computer-based retrieval strategy included the combination of the following terms: (1) "diabetes", "diabetes mellitus" or "glucose intolerance"; (2) "sperm", "semen", "male infertility", "spermatozoa", "semen analysis", "semen parameters" or "sperm quality". In addition, articles cited in the reference list were also reviewed.

### *Inclusion and exclusion criteria*

Articles were included in our study if they met the following criteria: (1) the experimental group included patients diagnosed with DM, and the control group included patients without DM; (2) semen samples were obtained before therapeutic intervention; (3) data were available and could be extracted from the article or obtained by calculation. Furthermore, if more than one article had been published using the same data, we selected the most complete or the most recent study. Major reasons for ex-

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**Table 1.** Characteristics of datasets included in this meta-analysis

Study	Year	Country	Sample size (case/Control)	Study design	Mean age (case/control)	Abstinence time (days)	DM classification	Semen parameters	NOS
Agbaje et al.	2007	England	27/29	Case-control	34.0±2.0/32.7±0.7	2-5	DM1	SV, SC, STM, SNM, STC, SDF	6
Ali et al.	1993	Pakistan	414/100	Case-control	54.0±16.5	1-1.5	DM1: 100 DM2: 314	SV, SC, STM, SNM	7
Bartak et al.	1975	Czechoslovakia	25/24	Case-control	18.5/18.7	4-7	DM1	SV, SC, SNM, STC	6
Bartak et al.	1979	Czechoslovakia	65/77	Case-control	44.1/46.7	4-7	NI	SV, SC, SNM, STC	6
Baccetti et al.	2002	Italy	22/24	Case-control	38±6/37±5	2-3	NI	SV, SC, SPM, STC	7
Bhattacharya et al.	2014	India	52/66	Prospective	36.29±5.29/34.92±4.58	NI	NI	SV, SC, STM, SRM, SNM, STC	7
Handelsman et al.	1985	Australia	28/21	Case-control	32.7±1.5/31.4±0.7	NI	DM1	SV, SC, STM	7
Karimi et al.	2012	Iran	32/35	Case-control	35.84±8.89/32.58±5.68	3-4	DM1: 17 DM2: 15	SV, SC, STM, SNM, STC, SDF	8
Kriegel et al.	2009	Germany	2/3	Case-control	30.0±9.9/32.58±5.68	3	DM1	SC, SPM, SNM, SDF	5
La Vignera et al.	2015	Italy	32/20	Case-control	27.0±1.3/28±0.9	3-5	DM1	SV, SC, SPM, SNM	5
Liu et al.	2015	China	296/20	Case-control	NI/NI	3-5	DM2	SPM	7
Mallidis et al.	2007	England	21/31	Case-control	37.6±9.5/34.6±5.4	2-5	DM1: 14 DM2: 7	SV, SC, STM, SNM, STC	5
Mallidis et al.	2009	England	13/9	Case-control	33.0±3.8/32.0±1.3	2-5	DM1	SV, SC, STM, SNM, STC	5
Eisenberg et al.	2015	USA	14/458	Prospective	>18/NI	2	NI	SV, SC, SNM, STC, SDF	8
Murray et al.	1988	USA	10/8	Case-control	23.0±0.8/26.0±1.7	NI	DM1	SV, SC, STM	6
Paasch et al.	2011	Germany	15/21	Case-control	45.0/25.8±5.6	3-7	DM1: 8 DM2: 7	SC, SPM, SNM, SDF	6
Padron et al.	1984	Cuba	32/42	Case-control	18.6/NI	3-7	DM1	SV, SC, STM, SNM	6
Rama et al.	2012	India	35/123	Prospective	34.25±4.18/33.73±3.40	2-5	DM2	SV, SC, STM, SPM, SRM, SNM, SDF	8
Shrivastav et al.	1989	England	18/15	Case-control	31/29	3-5	DM1	SV, SC, SNM	6
Singh et al.	2014	India	25/25	Case-control	47.8±3/44.3±2.3	NI	NI	SV, SC, STM, SNM	5
Vignera et al.	2012	Italy	40/20	Case-control	36.5±8.0/33.3±6.2	3-5	DM2	SV, SC, SPM, SNM, STC	8

Abbreviations: DM: diabetes mellitus; SV: semen volume; SC: sperm concentration; STM: total sperm motility; SPM: progressive sperm motility; SRM: rapid progressive sperm motility; SNM: normal sperm morphology; STC: total sperm count; SDF: sperm DNA fragmentation; NI: not indicated in the study; NOS: Newcastle-Ottawa Scale.

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**Table 2.** Detailed data of semen parameters in each included study (case/control; mean  $\pm$  SD)

Study	DM classification	SV	SC (million/mL)	STM (%)	SPM (%)	SRM (%)	SNM (%)	STC (million/ejaculate)	SDF (%)
Agbaje et al.	DM1	2.6 $\pm$ 0.3/3.3 $\pm$ 0.2	77.3 $\pm$ 30.1/ 57.5 $\pm$ 18.0	46.0 $\pm$ 4.2/ 47.3 $\pm$ 2.8	NI	NI	11.1 $\pm$ 0.6/11.7 $\pm$ 0.8	198 $\pm$ 87.8/173 $\pm$ 62.3	53 $\pm$ 3/32 $\pm$ 2
Ali et al.	Mixed	2.9 $\pm$ 0.94/3.5 $\pm$ 1.05	49.0 $\pm$ 35.7/ 52.0 $\pm$ 35.0	53.5 $\pm$ 15.3/ 55.5 $\pm$ 15.0	NI	NI	63.9 $\pm$ 15.7/64.5 $\pm$ 15.8	NI	NI
Bartak et al.	DM1	2.6 $\pm$ 1.4/2.8 $\pm$ 1.1	109 $\pm$ 64/ 113 $\pm$ 58	NI	NI	NI	57 $\pm$ 15/69 $\pm$ 7	257 $\pm$ 143/285 $\pm$ 118	NI
Bartak et al.	Not stated	2.78 $\pm$ 1.66/3.24 $\pm$ 1.81	135.15 $\pm$ 91.03/ 118.95 $\pm$ 61.45	NI	NI	NI	54.11 $\pm$ 17.69/60.55 $\pm$ 16.29	325.03 $\pm$ 244.40/ 354.34 $\pm$ 229.54	NI
Baccetti et al.	Not stated	3.3 $\pm$ 1.2/2.1 $\pm$ 1.2	43.4 $\pm$ 30/ 65 $\pm$ 50	NI	18 $\pm$ 11/60 $\pm$ 12	NI	NI	136 $\pm$ 89/201 $\pm$ 190	NI
Bhattacharya et al.	Not stated	2.26 $\pm$ 1.41/2.92 $\pm$ 1.11	77.6 $\pm$ 53.2/ 86.0 $\pm$ 43.0	49.83 $\pm$ 16.9/ 75.22 $\pm$ 13.68	NI	17.17 $\pm$ 12.25/ 45.27 $\pm$ 24.02	52.25 $\pm$ 12.34/45.71 $\pm$ 13.24	178.01 $\pm$ 151.79/ 242.11 $\pm$ 143.62	NI
Handelsman et al.	DM1	2.2 $\pm$ 0.4/3.1 $\pm$ 0.2	71.8 $\pm$ 14.3/ 83.9 $\pm$ 5.7	61 $\pm$ 5/69 $\pm$ 1	NI	NI	NI	NI	NI
Karimi et al.	Mixed	3.22 $\pm$ 1.47/3.64 $\pm$ 1.30	98.28 $\pm$ 54.76/ 87.00 $\pm$ 37.59	63.84 $\pm$ 8.37/ 67.51 $\pm$ 5.73	NI	NI	33.84 $\pm$ 3.27/35.25 $\pm$ 3.82	326.44 $\pm$ 233.71/ 311.31 $\pm$ 134.27	41.09 $\pm$ 9.55/ 19.22 $\pm$ 3.63
Kriegel et al.	DM1	NI	122.2 $\pm$ 103.0/ 74.9 $\pm$ 43.2	NI	53.3 $\pm$ 2.4/53.0 $\pm$ 3.4	NI	5.5 $\pm$ 0.7/10.3 $\pm$ 3.4	NI	8.8 $\pm$ 1.4/ 11.7 $\pm$ 1.9
La Vignera et al.	DM1	3.0 $\pm$ 3.3/2.5 $\pm$ 3.6	45.0 $\pm$ 2.5/ 50.0 $\pm$ 3.4	NI	10.0 $\pm$ 1.4/45.0 $\pm$ 1.4	NI	7.0 $\pm$ 1.0/8.0 $\pm$ 1.5	NI	NI
Liu et al.	DM2	NI	NI	NI	36.6 $\pm$ 14.2/67 $\pm$ 5.2	NI	NI	NI	NI
Mallidis et al.	Mixed	2.2 $\pm$ 1.2/3.8 $\pm$ 1.6	111.0 $\pm$ 58.9/ 78.6 $\pm$ 64.3	58.4 $\pm$ 16.1/ 51.5 $\pm$ 11.2	NI	NI	11.0 $\pm$ 3.5/12.0 $\pm$ 3.8	237.0 $\pm$ 173.6/ 271.4 $\pm$ 206.5	NI
Mallidis et al.	DM1	3.3 $\pm$ 0.6/3.1 $\pm$ 0.3	148.3 $\pm$ 60.9/ 74.5 $\pm$ 20.8	49.8 $\pm$ 0.8/ 53.1 $\pm$ 4.7	NI	NI	12.0 $\pm$ 0.6/13.8 $\pm$ 1.3	430.8 $\pm$ 81.9/219 $\pm$ 68.7	NI
Eisenberg et al.	Not stated	2.6 $\pm$ 1.4/3.4 $\pm$ 1.5	72.9 $\pm$ 57.6/ 74.1 $\pm$ 54.3	NI	NI	NI	29.8 $\pm$ 10/30.4 $\pm$ 12.5	159.2 $\pm$ 116.9/ 236.9 $\pm$ 180.3	10.1 $\pm$ 5/ 15.5 $\pm$ 10.4
Murray et al.	DM1	2.25 $\pm$ 0.6/2.98 $\pm$ 0.7	41.5 $\pm$ 10.7/ 57.4 $\pm$ 10.7	46.3 $\pm$ 6.1/ 53.5 $\pm$ 4.4	NI	NI	NI	NI	NI
Paasch et al.	DM1	NI	107.8 $\pm$ 99.4/ 92.0 $\pm$ 52.6	NI	40.8 $\pm$ 9.5/52.1 $\pm$ 4.4	NI	4.0 $\pm$ 3.4/10.8 $\pm$ 4.9	NI	19.8 $\pm$ 17.1/ 7.5 $\pm$ 5.4
	DM2	NI	143.4.8 $\pm$ 74.4/ 92.0 $\pm$ 52.6	NI	41.4 $\pm$ 6.3/52.1 $\pm$ 4.4	NI	5.7 $\pm$ 3.8/10.8 $\pm$ 4.9	NI	19.0 $\pm$ 19.9/ 7.5 $\pm$ 5.4
Padron et al.	DM1	2.1 $\pm$ 0.2/2.8 $\pm$ 0.2	78.1 $\pm$ 9.6/ 93.1 $\pm$ 11.0	46.62.9/ 78.6 $\pm$ 1.8	NI	NI	62.5 $\pm$ 1.8/66.5 $\pm$ 2.4	NI	NI
Rama et al.	DM2	2.05 $\pm$ 1.35/2.11 $\pm$ 1.19	97.13 $\pm$ 84.72/ 104.46 $\pm$ 76.65	66.59 $\pm$ 19.6/ 66.33 $\pm$ 19.8	45.50 $\pm$ 18.0/ 46.97 $\pm$ 18.14	14.64 $\pm$ 9.60/ 17.99 $\pm$ 11.51	9.67 $\pm$ 5.92/10.96 $\pm$ 6.39	NI	37.05 $\pm$ 12.68/ 21.03 $\pm$ 10.13
Shrivastav et al.	DM1	2.8 $\pm$ 2.1/2.6 $\pm$ 0.7	110.1 $\pm$ 49.3/ 80.0 $\pm$ 55.3	NI	NI	NI	57 $\pm$ 10/73 $\pm$ 4	NI	NI
Singh et al.	DM2	2.2 $\pm$ 1.1/2.4 $\pm$ 0.3	24.6 $\pm$ 2.1/ 42.7 $\pm$ 4.6	52.3 $\pm$ 1.3/ 69.1 $\pm$ 3.2	NI	NI	31.5 $\pm$ 1.2/47.2 $\pm$ 3.7	NI	NI
Vignera et al.	DM2	4.6 $\pm$ 1.4/5.1 $\pm$ 1.7	10.8 $\pm$ 4.9/ 63.1 $\pm$ 17.3	46.0 $\pm$ 4.2/ 47.3 $\pm$ 2.8	13.4 $\pm$ 5.5/36.7 $\pm$ 5.5	NI	10.9 $\pm$ 6.7/30.1 $\pm$ 4.5	51.4 $\pm$ 31.1/ 331.1 $\pm$ 165.8	NI

Abbreviations: DM: diabetes mellitus; SV: semen volume; SC: sperm concentration; STM: total sperm motility; SPM: progressive sperm motility; SRM: rapid progressive sperm motility; SNM: normal sperm morphology; STC: total sperm count; SDF: sperm DNA fragmentation; NI: not indicated in the study.

overall estimate. To explain the source of heterogeneity, subgroup analyses were conducted based on the DM classification, country, sample size and year of publication. In addition, the Begg and Mazumdar adjusted rank correlation and the Egger regression asymmetry tests were conducted to detect publication bias. All the *P* values were for two-sided tests, and  $P < 0.05$  was considered statistically significant. All statistical analyses were performed with the STATA software package version 12.0 (STATA Corporation, College Station, Texas, USA) and the Cochrane Collaboration (RevMan 5.2, Copenhagen, Denmark).

### Results

#### *Characteristics of the included studies*

A flow chart of the study selection progress is shown in **Figure 1**. In all, 2787 potential studies were identified from the databases; of these, 587 duplicate articles were excluded. After screening the abstracts or titles, 2134 articles were excluded. These articles were not associated with our study ( $n=1294$ ) or were reviews ( $n=298$ ), animal studies ( $n=444$ ), case reports ( $n=54$ ), guidelines ( $n=6$ ), comments ( $n=12$ ), letters ( $n=8$ ), or non-English articles ( $n=11$ ). A total of 53 potentially eligible studies were further identified through a full-text evaluation. In addition, 32 other articles were excluded from our study due to the following reasons: no usable data ( $n=10$ ), duplicate data ( $n=1$ ) and an irrelevant conclusion ( $n=21$ ). Finally, a total of 21 articles involving 1218 cases and 1171 participants were included in this meta-analysis [1, 4, 6, 7, 9, 11-26]. Regarding the DM classification, 7 studies were conducted with the type 1 DM (DM1) participants [1, 4, 9, 17, 21, 24, 26], 4 studies were conducted with type 2 DM (DM2) participants [18, 19, 23, 25], and 4 studies were conducted with DM1 and DM2 participants [6, 16, 20, 22]; the remaining 6 studies did not report this information [2, 11-15]. The characteristics of each study are summarised in **Table 1**. Detailed data of semen parameters in each included study are summarised in **Table 2**.

#### *Meta-analysis*

Eight semen parameters (i.e., semen volume, sperm concentration, total sperm motility, progressive sperm motility, rapid progressive

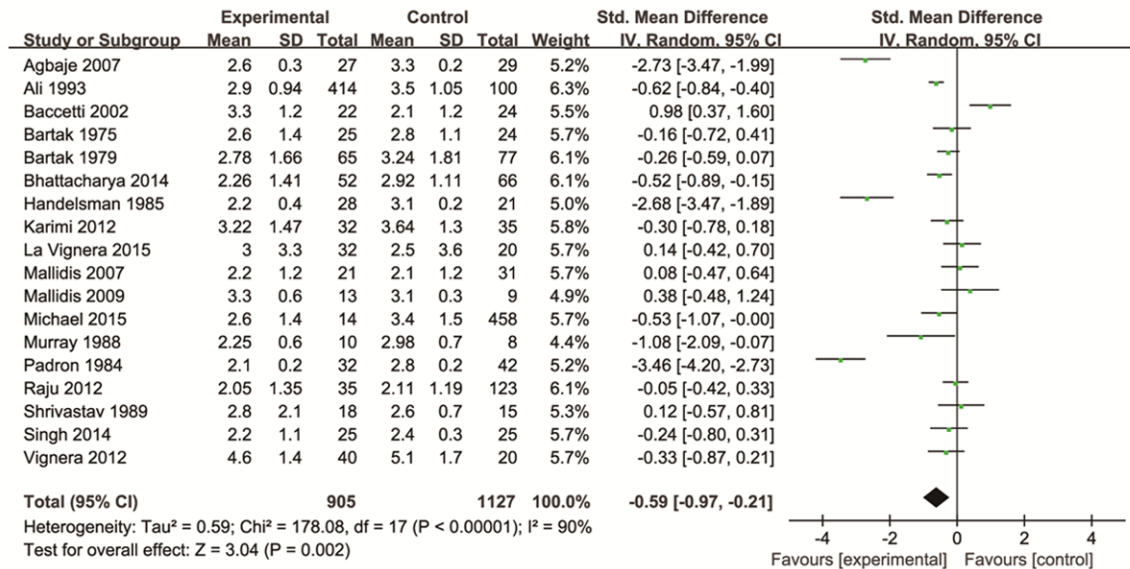
sperm motility, normal sperm morphology, total sperm count, and sperm DNA fragmentation) were individually analysed using a random-effects model to estimate the effect of DM on each parameter. The results suggested that semen volume, sperm concentration, total sperm motility, progressive sperm motility, and normal sperm morphology were significantly lower in DM patients than in nondiabetic controls, and the pooled SMDs (95% CIs) were  $-0.59$  [ $-0.97, -0.21$ ],  $-0.52$  [ $-0.94, -0.09$ ],  $-1.93$  [ $-2.79, -1.08$ ],  $-3.54$  [ $-5.25, -1.83$ ], and  $-1.08$  [ $-1.53, -0.62$ ], respectively,  $P < 0.05$  (**Figures 2-5, 7**). In addition, sperm DNA fragmentation was significantly higher in DM patients than in nondiabetic controls, and the pooled SMD (95% CI) was  $1.99$  [ $0.41, 3.56$ ],  $P < 0.05$  (**Figure 9**). However, rapid progressive sperm motility and total sperm count in DM patients were not significantly different from those in nondiabetic controls (SMDs (95% CIs)  $-0.85$  [ $-1.95, 0.24$ ] and  $-0.23$  [ $-0.71, 0.25$ ], respectively,  $P > 0.05$ ; **Figures 6 and 8**). There was evidence of significant heterogeneity among these studies ( $P > 0.05$ ,  $I^2 > 50\%$ ).

The effects of DM on semen parameters revealed by the subgroup analyses based on DM classification, country, sample size, year of publication and study design are summarised in **Table 3**. Sensitivity analyses were performed to find the origin of heterogeneity in all semen parameters, and none of the corresponding pooled SMDs were significantly changed, which suggested that the results were statistically stable and reliable. **Figure 10** shows the sensitivity analysis results for semen volume. The other sensitivity analysis results are not shown due to the limited available space. Both the Begg and Egger tests were performed to evaluate the publication bias of the studies, no obvious publication bias was found.

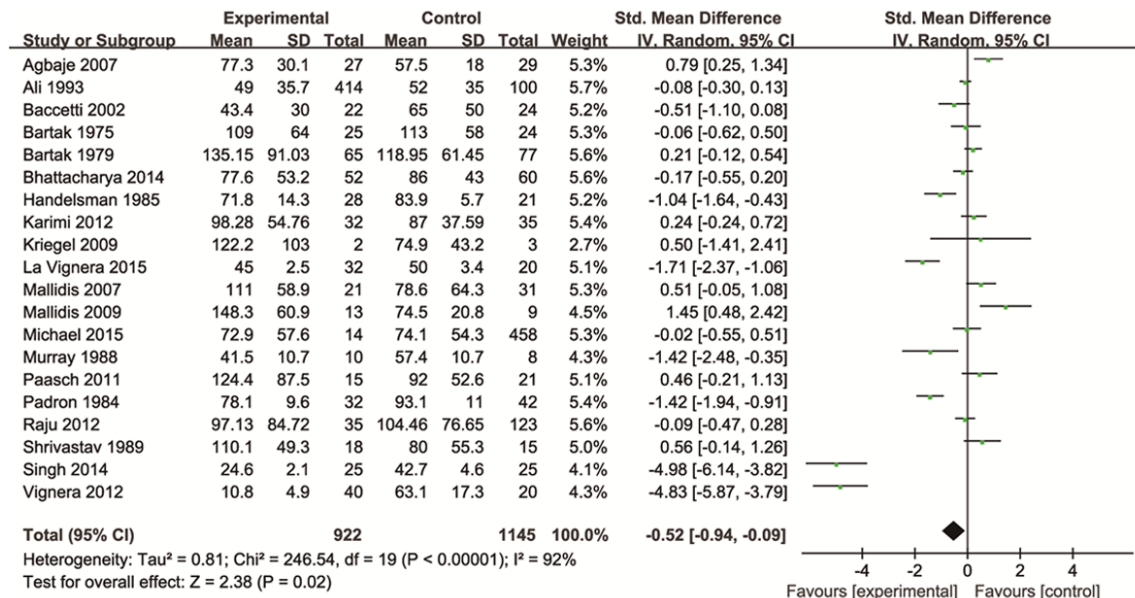
### Discussion

In this study, 21 available published articles were statistically analysed to investigate the effects of DM on semen parameters. Our results suggested that DM significantly reduced the sperm volume, sperm concentration, total sperm motility, progressive sperm motility, and normal sperm morphology and increased sperm DNA fragmentation. However, no effects of DM on rapid progressive sperm motility and

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**Figure 2.** Forest plot of the effect of DM on semen volume (from 18 trials [1, 4, 6, 7, 9, 11-16, 18, 20, 21, 23-26], 1127 patients in the control group, 905 patients in the experimental group). Data are shown as the mean and 95% confidence interval. The random-effects model was applied. Semen volume was significantly lower in DM patients than in nondiabetic controls.

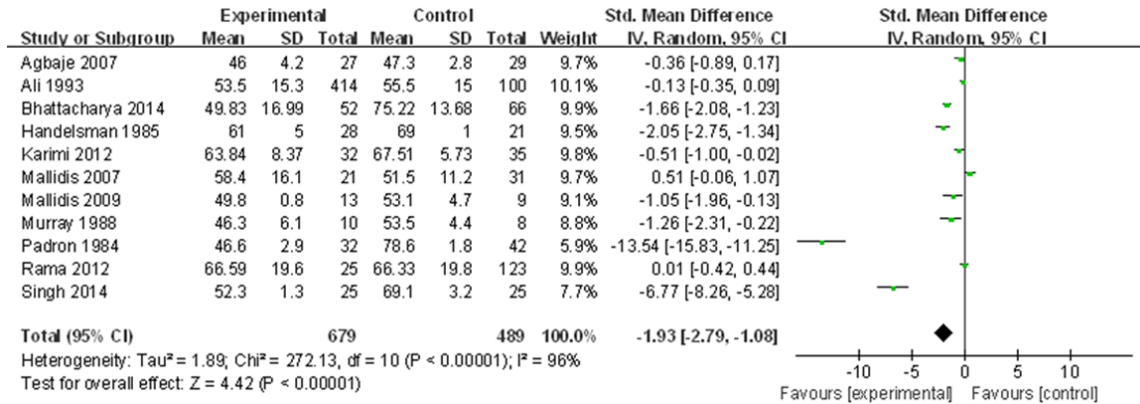


**Figure 3.** Forest plot of the effect of DM on sperm concentration (from 20 trials [1, 4, 6, 7, 9, 11-18, 20-26], 1145 patients in the control group, 922 patients in the experimental group). Data are shown as the mean and 95% confidence interval. The random-effects model was applied. Semen concentration was significantly lower in DM patients than in nondiabetic controls.

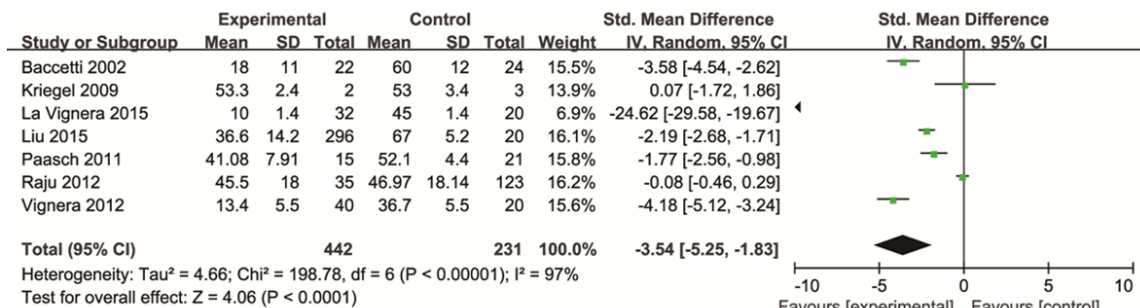
the total sperm count were identified. Evidence of heterogeneity among these studies was observed, which was partially explained by the following features: 1. inconsistent DM types; 2. differences in participant age, disease duration and control blood glucose levels; 3. inconsis-

tent standard units for measuring semen parameters (semen analysis is a partially subjective process that requires skill and is inherently difficult to standardise); 4. an apparent decline in semen quality in recent decades; 5. different participant populations; 6. the use of

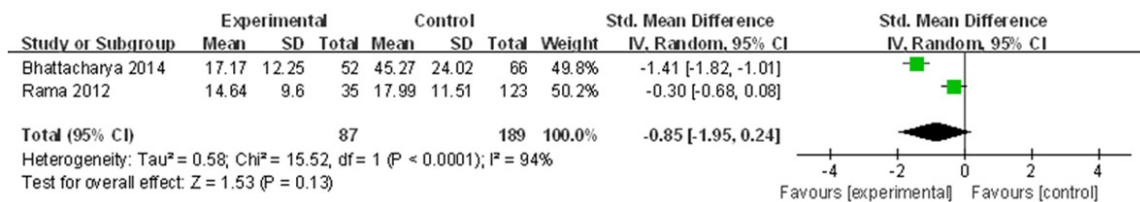
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**Figure 4.** Forest plot of the effect of DM on total sperm motility (from 11 trials [1, 4, 6, 9, 14-16, 20, 21, 23, 25], 489 patients in the control group, 679 patients in the experimental group). Data are shown as the mean and 95% confidence interval. The random-effects model was applied. Total sperm motility was significantly lower in DM patients than in nondiabetic controls.



**Figure 5.** Forest plot of the effect of DM on progressive sperm motility (from 7 trials [11, 17-19, 22, 23, 26], 231 patients in the control group, 442 patients in the experimental group). Data are shown as the mean and 95% confidence interval. The random-effects model was applied. Progressive sperm motility was significantly lower in DM patients than in nondiabetic controls.



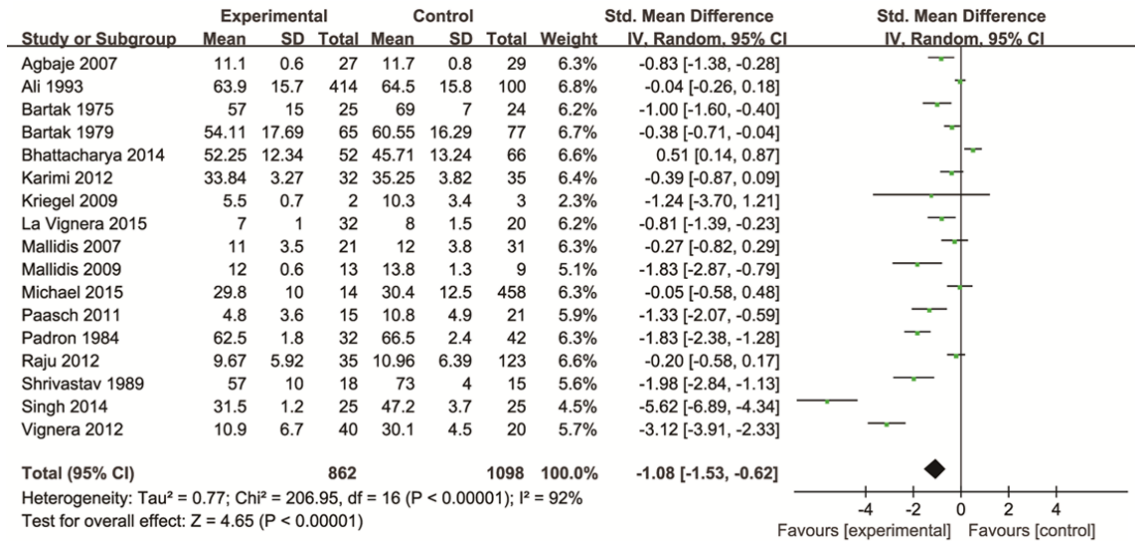
**Figure 6.** Forest plot of the effect of DM on rapid progressive sperm motility (from 2 trials [14, 23], 189 patients in the control group, 87 patients in the experimental group). Data are shown as the mean and 95% confidence interval. The random-effects model was applied. Rapid progressive sperm motility in DM patients was not significantly different from that in nondiabetic controls.

a case-control study design in most but not all studies.

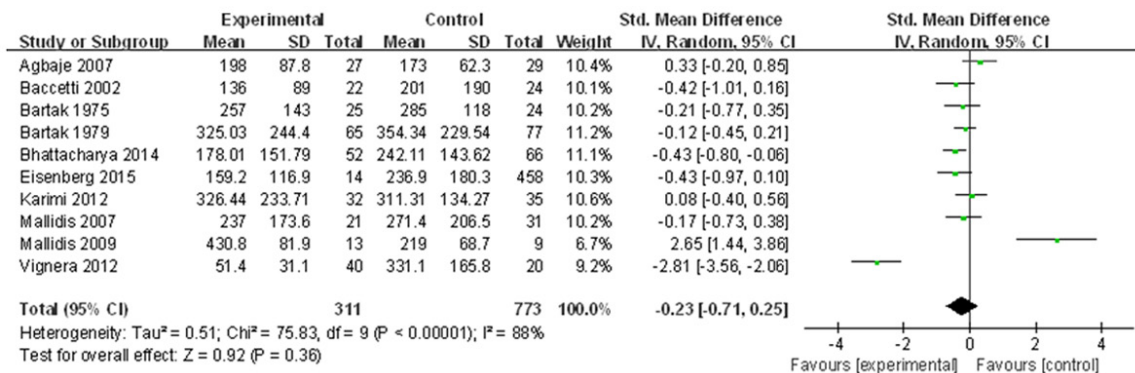
DM is a complex metabolic disorder that presents in two major forms, DM1 and the more common DM2. DM1, or insulin-dependent DM, is usually caused by an autoimmune reaction in which the body's defence system attacks insu-

lin-producing pancreatic beta cells in genetically susceptible individuals. On the other hand, DM2 is characterised by insulin resistance and responsible for the vast majority of all DM cases. It has been reported that 51% of all diabetic male individuals have some degree of subfertility and/or infertility [27]. Delfino et al. reported that in 510 partners of infertile cou-

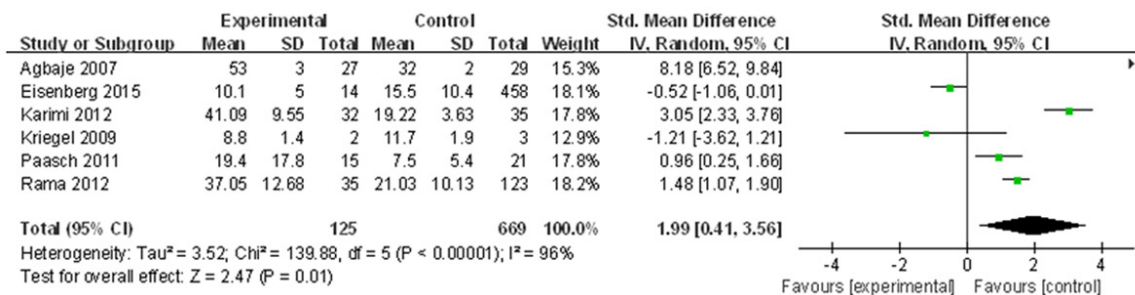
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**Figure 7.** Forest plot of the effect of DM on normal sperm morphology (from 17 trials [1, 4, 6, 7, 9, 12-14, 16-18, 20, 22-26], 1098 patients in the control group, 862 patients in the experimental group). Data are shown as the mean and 95% confidence interval. The random-effects model was applied. Normal sperm morphology was significantly lower in DM patients than in nondiabetic controls.



**Figure 8.** Forest plot of the effect of DM on total sperm count (from 10 trials [1, 4, 7, 11-14, 16, 18, 20], 773 patients in the control group, 311 patients in the experimental group). Data are shown as the mean and 95% confidence interval. The random-effects model was applied. Total sperm count in DM patients was not significantly different from than in nondiabetic controls.



**Figure 9.** Forest plot of the effect of DM on sperm DNA fragmentation (from 6 trials [4, 7, 16, 17, 22, 23], 669 patients in the control group, 125 patients in the experimental group). Data are shown as the mean and 95% confidence interval. The random-effects model was applied. Sperm DNA fragmentation was significantly higher in DM patients than in nondiabetic controls.



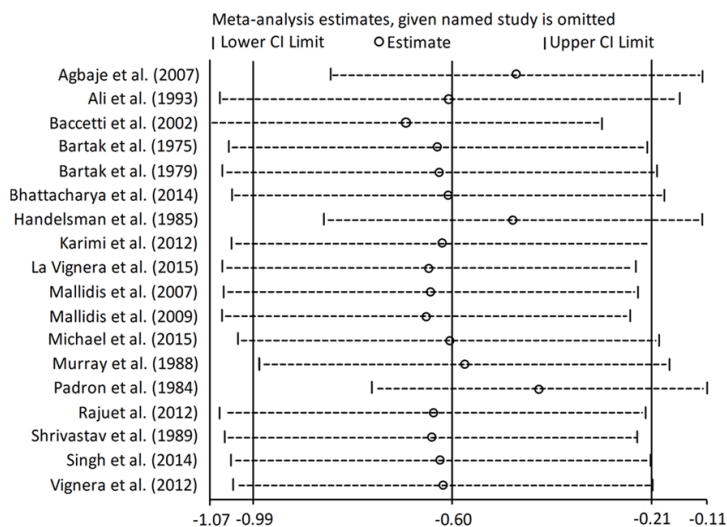
## Effects of diabetes mellitus on semen quality

**Table 3.** Subgroup analyses of the association between DM and semen parameters

Subgroup	Number of studies	SV	SC	STM	SPM	SRM	SNM	STC	SDF	
DM classification	DM1	9	-1.20 (-2.28, -0.11)	-0.24 (-0.94, 0.46)	-3.38 (-5.59, -1.17)	-8.23 (-15.67, -0.79)	NI	-1.36 (-1.74, -0.98)	0.82 (-0.42, 2.06)	2.66 (-2.48, 7.79)
	DM2	5	-0.17 (-0.44, 0.10)	-2.26 (-4.99, 0.46)	-2.01 (-3.74, -0.28)	-2.14 (-3.85, -0.43)	-0.30 (-0.68, 0.08)	-2.49 (-4.65, -0.33)	-2.85 (-3.59, -2.10)	1.42 (1.05, 1.79)
	Mixed	3	-0.54 (-0.82, -0.26)	0.15 (-0.21, 0.52)	-0.01 (-1.02, 1.00)	NI	NI	-0.12 (-0.32, 0.07)	-0.03 (-0.39, 0.33)	3.08 (2.37, 3.80)
	Not stated	4	-0.09 (-0.55, 0.38)	-0.08 (-0.36, 0.21)	-1.67 (-2.09, -1.25)	-3.64 (-4.60, -2.69)	-1.42 (-1.83, -1.02)	0.03 (-0.55, 0.60)	-0.31 (-0.52, -0.10)	-0.52 (-1.06, 0.01)
Country	Asia	6	-0.39 (-0.62, -0.16)	-0.78 (-1.54, -0.01)	-1.53 (-2.58, -0.48)	-1.13 (-3.21, 0.94)	-0.85 (-1.95, 0.24)	-0.87 (-1.71, -0.03)	-0.20 (-0.70, 0.30)	2.26 (0.70, 3.81)
	Europe	11	-0.19 (-0.73, 0.36)	-0.21 (-0.94, 0.51)	-0.26 (-1.09, 0.58)	-5.41 (-8.19, -2.63)	NI	-1.27 (-1.80, -0.73)	-0.17 (-0.93, 0.59)	2.56 (-2.56, 7.69)
	Other	4	-1.97 (-3.47, -0.47)	-0.96 (-1.70, -0.23)	-5.52 (-10.15, -0.89)	NI	NI	-0.95 (-2.71, 0.82)	-0.43 (-0.97, 0.10)	-0.52 (-1.06, 0.01)
Sample size	≥50	13	-0.69 (-1.11, -0.27)	-0.83 (-1.42, -0.25)	-2.18 (-3.24, -1.13)	-5.52 (-8.23, -2.81)	-0.85 (-1.95, 0.24)	-0.95 (-1.48, -0.43)	-0.47 (-1.01, 0.07)	2.93 (0.74, 5.12)
	<50	8	-0.40 (-1.42, 0.63)	-0.04 (-0.64, 0.57)	-1.57 (-2.21, -0.93)	-1.92 (-3.70, -0.14)	NI	-1.46 (-1.88, -1.05)	0.58 (-0.82, 1.98)	-0.12 (2.67, 2.43)
Year of publication	After 2000	14	-0.28 (-0.70, 0.15)	-0.60 (-1.29, 0.10)	-1.23 (-2.19, -0.28)	-3.62 (-5.36, -1.89)	-0.85 (-1.95, 0.24)	-1.20 (-1.86, -0.54)	-0.22 (-0.88, 0.45)	1.99 (0.41, 3.56)
	Before 2000	7	-1.14 (-1.90, -0.39)	-0.42 (-0.92, 0.08)	-3.96 (-6.67, -1.24)	NI	NI	-1.00 (-1.71, -0.29)	-0.15 (-0.43, 0.14)	NI
Study design	Case-control	18	-0.42 (-0.80, -0.05)	-0.62 (-1.16, 0.10)	-2.37 (-3.48, -1.25)	-4.31 (-6.21, -2.41)	NI	-1.42 (-1.96, -0.87)	-0.15 (-0.80, 0.50)	2.72 (-0.03, 5.47)
	Prospective	3	-1.49 (-3.07, 0.09)	-0.11 (-0.35, 0.12)	-0.83 (-2.48, -0.82)	-0.08 (-0.46, -0.29)	-0.85 (-1.95, 0.24)	0.10 (-0.37, 0.56)	-0.43 (-0.74, -0.13)	0.49 (-1.49, 2.47)

Abbreviations: DM: diabetes mellitus; SV: semen volume; SC: sperm concentration; STM: total sperm motility; SPM: progressive sperm motility; SRM: rapid progressive sperm motility; SNM: normal sperm morphology; STC: total sperm count; SDF: sperm DNA fragmentation; NI: not indicated in the study.

## Effects of diabetes mellitus on semen quality



**Figure 10.** Sensitivity analysis of the effect of DM on semen volume. The result was statistically stable and reliable.

ples, the prevalence of DM was 1.18% [28]. The prevalence of primary (16%) and secondary (19.1%) infertility was significantly higher in patients with DM than in patients without DM. One of the major factors contributing to subfertility and/or infertility in male DM individuals with DM is the defective sperm quality due to abnormal sperm parameters, such as concentration, motility, morphology and DNA fragmentation [29]. Semen analysis is an imperfect tool, but it remains the cornerstone of the investigation of male infertility. The World Health Organization (WHO) manual has been a vital tool in the endeavour to achieve consistent semen analysis standards across the world. There are 5 versions of the manual; the first edition was published in 1980 and the fifth edition was published in 2010.

A certain semen volume is necessary to transport the sperm into the female reproductive tract, thus, semen volume is an important indicator of semen quality. In the fifth version of the WHO manual, the lower reference limit for semen volume is 1.5 mL [30]. In all, 18 studies were included in our study and the results showed that semen volume was significantly lower in the patients with DM than in the non-diabetic controls. Because most of the semen volume is from the testicles, a reduction in semen volume may be related to decreased testicular weight in DM [31]. This finding could also possibly be attributed to autonomic neuropathy and its related erectile and ejaculatory dysfunc-

tions associated with long-standing diabetic complications [23].

Subfertility and/or infertility is closely related to the sperm concentration [31]. Several animal studies showed that DM led to a marked reduction in fecundity by decreasing sperm concentration [10]. There is a decrease in male fertility when the sperm concentration is below the normal threshold value ( $15 \times 10^6/\text{ml}$ – $55 \times 10^6/\text{ml}$ ) [32]. The results of our study showed that the sperm concentration was lower in patients with DM than in the controls. Sperm concentration is dependent on total sperm count and semen volume; thus, any factors that change the total

sperm count and semen volume can affect the sperm concentration. The total sperm count is dependent on the balance of sperm production/death. There are studies suggesting that spermatogenesis disruption and germ cell apoptosis in DM are related to local autoimmune damage [33]. Insulin stimulates several of the Leydig cell functions, which may affect the outcome of spermatogenesis [34]. DM patients usually present high levels of oxidative stress (OS) and, consequently, reactive oxygen species (ROS) overproduction and decreased antioxidant levels [35]. In contrast to other cells, sperm cells are particularly susceptible to OS in their plasma membranes due to the presence of a high concentration of polyunsaturated fatty acids in the membrane [36]. Apoptosis is another problem resulting from OS in association with DM [37]. DM also provokes severely detrimental blood-testis barrier alterations, which may be responsible for spermatogenesis disruptions [38]. Moreover, epidermal growth factor deficiency is a potential cause of the pathogenesis of oligozoospermia in diabetic mice [39]. Interestingly, in our meta-analysis, although semen volume and sperm concentration were lower in patients with DM than in patients without DM, the associations between DM and total sperm count were not identified. More studies related to the effect of DM on the total sperm count are needed.

The fifth version of the WHO manual stipulated that the lower reference limits for total sperm

motility and progressive sperm motility were 40% and 32%, respectively, and that males with sperm motility values below these threshold values are considered to have asthenozoospermia [30]. Semen motility is essential for sperm to reach the female reproductive tract and result in fertilisation. In our study, total and progressive sperm motility were significantly lower in the patients with DM than in the nondiabetic controls. The decreased motility observed in DM patients might be attributed to the increased ROS levels, altered mitochondrial DNA [23], or an abnormal glucose metabolism [40]. Reduced levels of glyceraldehyde-3-phosphate dehydrogenase are associated with the actions of ROS, which affect sperm motility and block progressive sperm movement [19]. Due to a lack of glucose transporters 9 protein and insulin, an abnormal glucose metabolism with DM can cause a significant reduction in sperm motility [40]. Moreover, the impaired sperm motility may be due to the decreased bioavailability of testosterone and epididymal secretory products [41]. It is worth noting that no correlations have been found between sperm motility and age, age of DM onset, DM duration or glycated haemoglobin [8]. In our study, an association between DM and rapid progressive sperm motility was not identified because only two studies reported these effects, which limited the statistical power.

Sperm morphology is the single most important source of information on the reproductive potential of spermatozoa [42]. In our study, 17 articles reported an association between DM and sperm morphology, and DM had a negative effect on sperm morphology. The very low cut-off value for sperm morphology of 4% morphologically normal spermatozoa, as proposed in the fifth version of the WHO manual [30], is in agreement with recently published values [42, 43] and with the trend in declining mean normal sperm morphology values reported in the literature [44]. Sperm morphology is impaired by specific conditions, such as workplace-related exertion and hypertension [7]. A significant increase in abnormal sperm morphology has been reported in prediabetic rats [45]. Several studies have shown that DM leads to a marked reduction in fecundity by altering the normal morphology of sperm cells [13, 28, 46]. Increased OS is also harmful to sperm morphology and is considered a main factor of decreased of normal sperm morphology in DM

[46]. Increased lipid peroxidation in patients with DM with poor metabolic control is also associated with low normal sperm morphology [18].

Various studies have shown that fertility declines when sperm DNA fragmentation is elevated, i.e., is >30% [47]. The integrity of sperm DNA is an important value for the prediction of male fertility potential, and it may serve as a useful biomarker in the correction of detrimental, fertility-impairing conditions, such as varicocele [48]. Decreased sperm DNA integrity has been shown to be associated with impaired embryonic development, an increased incidence of spontaneous abortion, and the onset of certain childhood diseases [49]. In our meta-analysis, 6 articles reported an association between DM and sperm DNA fragmentation, and the patients with DM were found to have a higher percentage of sperm with DNA fragmentation than the nondiabetic controls. The high DNA fragmentation can potentially be attributed to DM-mediated OS. Several studies have also shown that oxidative damage to sperm DNA is associated with higher ROS levels in DM patients than in nondiabetic controls [50]. Moreover, sperm DNA is particularly susceptible to attack by ROS because of their high unsaturated fatty acid content and the absence of DNA repair mechanisms. Sperm DNA damage in DM patients promoted by ROS is suggested to be directly mediated by advanced glycation end products [20]. Amiri et al. reported that ROS-induced DNA damage was correlated with 8-hydroxydeoxyguanosine levels [51].

In our meta-analysis, 21 studies involved relatively high numbers of cases and controls were included, which strengthened the reliability and conclusiveness of our results. The findings of our study suggest that DM has a negative effect on sperm volume, sperm concentration, total sperm motility, progressive sperm motility, and normal sperm morphology and a positive effect on sperm DNA fragmentation. Drug that can improve sperm volume, sperm concentration, total sperm motility, progressive sperm motility, normal sperm morphology and DNA integrity may be able to help men who are sub- or infertile due to DM. However, our study also has some limitations. First, as most studies were based on a case-control design, selection bias

was inevitable. Second, semen analysis is inherently difficult to standardise across different studies. Third, only studies published in English were included in our study, which excluded data published in other languages. Finally, there is strong evidence of heterogeneity among the included studies. Although we detected a major source of heterogeneity by conducting sensitivity analyses, other differences between the studies should be considered.

Our study indicated that DM had negative effects on semen quality (i.e., sperm volume, sperm concentration, total sperm motility, progressive sperm motility, normal sperm morphology, and sperm DNA fragmentation). Furthermore, larger studies are needed to evaluate the causative mechanisms responsible for these changes as well as possible treatment options.

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### Disclosure of conflict of interest

None.

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