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Review

# Glycaemic control during the lockdown for COVID-19 in adults with type 1 diabetes: A meta-analysis of observational studies

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ABSTRACT

*Aims:* To assess the effects of lockdown due to COVID-19 pandemic on glucose metrics, measured by glucose monitoring systems, in adult individuals with type 1 diabetes.

*Methods:* We conducted a systematic literature search for English language articles from MEDLINE, Scopus and Web of Science up to February 28, 2021, using "diabetes", "lockdown", and "glucose" as key search terms. Time in range (TIR) was the main outcome; other metrics were time above range (TAR), time below range (TBR), mean blood glucose (MBG) and its variability (%CV), estimated HbA1c (eA1c) or glucose management indicator (GMI).

*Results:* Seventeen studies for a total of 3,441 individuals with type 1 diabetes were included in the analysis. In the lockdown period, TIR 70–180 mg/dl increased by 3.05% (95% CI 1.67–4.43%; $p < 0.0001$) while TAR (>180 mg/dL and > 250 mg/dL) declined by 3.39% (−5.14 to −1.63%) and 1.96% (−2.51 to −1.42%), respectively ($p < 0.0001$ for both). Both TBR < 70 and <54 mg/dL remained unchanged. MBG slightly decreased by 5.40 mg/dL (−7.29 to −3.51 mg/dL; $p < 0.0001$) along with a reduction in %CV. Pooled eA1c and GMI decreased by 0.18% (−0.24 to −0.11%; $p < 0.0001$) and a similar reduction was observed when GMI alone was considered (0.15%, −0.23 to −0.07%; $p < 0.0001$). Sensor use was only slightly but not significantly reduced during lockdown.

*Conclusions:* This meta-analysis shows that well-controlled people with type 1 diabetes on both MDI and CSII with continuous or flash glucose monitoring did not experience a deterioration in glucose control throughout the COVID-19 lockdown, showing a modest, though statistically significant improvement in many glucose control parameters.

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## Contents



## 1. Introduction

The World Health Organization (WHO) declared the outbreak of Coronavirus Disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) a public health emergency of international concern on January 30th, 2020, and a pandemic on March 11th, 2020 [1,2]. Right after that, many countries implemented mobility restrictions to limit the spreading of the pandemic, and in March many European countries entered a lockdown with severe limitations of people's movement, including outdoor physical activity and access to hospitals and health services for routine care. This has resulted in drastic changes in everyone's daily habits, family, social, and work relationships.

Diabetes ranks among the most prevalent comorbidities in subjects with COVID-19, after cardiovascular diseases [3]. People with diabetes are up to three times more likely than non-diabetic subjects to develop a more severe COVID-19 with increased need for admission to ICU, mechanical ventilation as well as higher mortality [3,4]. The perception of belonging to a highly vulnerable population entails a severe emotional impact in people with diabetes. Moreover, because of the lockdown, one could expect an increased sedentary behaviour, poorer diet adherence, more physiological stress that could affect daily management of chronic diseases like diabetes [5,6] and undermine glycaemic control, especially in subjects on complex insulin therapy, such as those with type 1 diabetes. In these individuals, achievement of glycaemic control is a complex task requiring multiple daily activities, including glucose monitoring and adequate insulin dose titration. This process has become easier and more effective by continuous glucose monitoring (CGM) or flash continuous monitoring (FGM) systems and data uploading on online platforms. These large repositories of glucose control data have offered a unique opportunity to explore the impact of the lockdown on glycaemic control in patients with type 1 diabetes. At variance of what was expected, rather than a worsening a trend toward improved glycaemic control has been reported. However, most of these studies included a limited number of participants so that the true impact of the lockdown in people with type 1 diabetes remains inconclusive.

Therefore, we have performed an updated systematic review and meta-analysis of studies assessing the effects of lockdown during COVID-19 pandemic on glucose metrics in adult subjects with type 1 diabetes using CGM or FGM.

## 2. Methods

### 2.1. *Information sources and study selection*

We conducted a systematic literature search on Medline, Scopus and Web of Science for articles published in English up to 28 February 2021 using the key search terms "diabetes", "lockdown", and "glucose". We reviewed all abstracts obtained from the search, examined reference lists to check for additional potentially relevant publications and obtained full text of all articles. A systematic review and meta-analysis were then conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [7]. Protocol of this meta-analysis has been submitted for registration to PROSPERO #CRD42021266936 (https://www.crd.york.ac.uk/PROSPERO/).

Prespecified inclusion criteria were 1) cohort observational studies of adult patients with type 1 diabetes exploring the impact of lockdown on glucose control; and 2) studies based on data obtained by CGM or FGM. Studies were excluded if they 1) included children, adolescents, or pregnant women, 2) included only subjects with type 2 diabetes, 3) glycaemic

control was assessed by self-monitoring blood glucose (SMBG) or self-reported. Eligible studies had to provide at least the following information: age, type of diabetes, pre- and during-lockdown periods of observation, type of glucose monitoring (CGM and/or FGM), percentage of time in range (TIR; 70–180 mg/dL) and/or other relevant glucose metrics [8–10].

The systemic search for literature was conducted by two independent investigators (MG and GP) and retrieved articles were independently examined for eligibility by the same investigators. Conflicts were resolved by consensus with a third investigator (SDP). Data were extracted by using predetermined forms and mainly included: first author, year of publication, country where the study was performed, periods of observation, type of diabetes, sample size, type of glucose monitoring (CGM or FGM), type of therapy (CSII or MDI), pre- and during-lockdown TIR and/or other glucose metrics including time above range (TAR; >180 mg/dL and >250 mg/dL), time below range (TBR; <70 mg/dL and <54 mg/dL), glucose variability estimated as coefficient of variation (%CV), average glucose (mg/dL), glucose management indicator (GMI) or estimated HbA1c (eA1c) [11], and percentage of sensor use (%).

The risk of bias for each study (**Supplementary** Table 1), was evaluated by the Newcastle-Ottawa Scale [12]. To be considered a high-quality study, ≥3 stars (score) in the selection domain and ≥ 1 star in the comparability domain, and ≥2 stars in the outcome domain were required.

### 2.2. *Statistical analysis*

We tabulated the characteristics of all included studies. The Comprehensive Meta-Analysis software V3 (Biostat, Englewood, NJ, USA) was employed to perform the meta-analyses using mean, standard deviation (SD; pre- and post-data) and sample size. Statistical heterogeneity of studies was assessed using $I^2$ index (<50%, 50–75%, and >75% represent low, moderate, and high heterogeneity, respectively). We analysed the results pooling differences in means and lower and upper limits (95% confidence interval, CI) by the random effect model to minimize the heterogeneity or between-study variance because the included studies differed to some extent

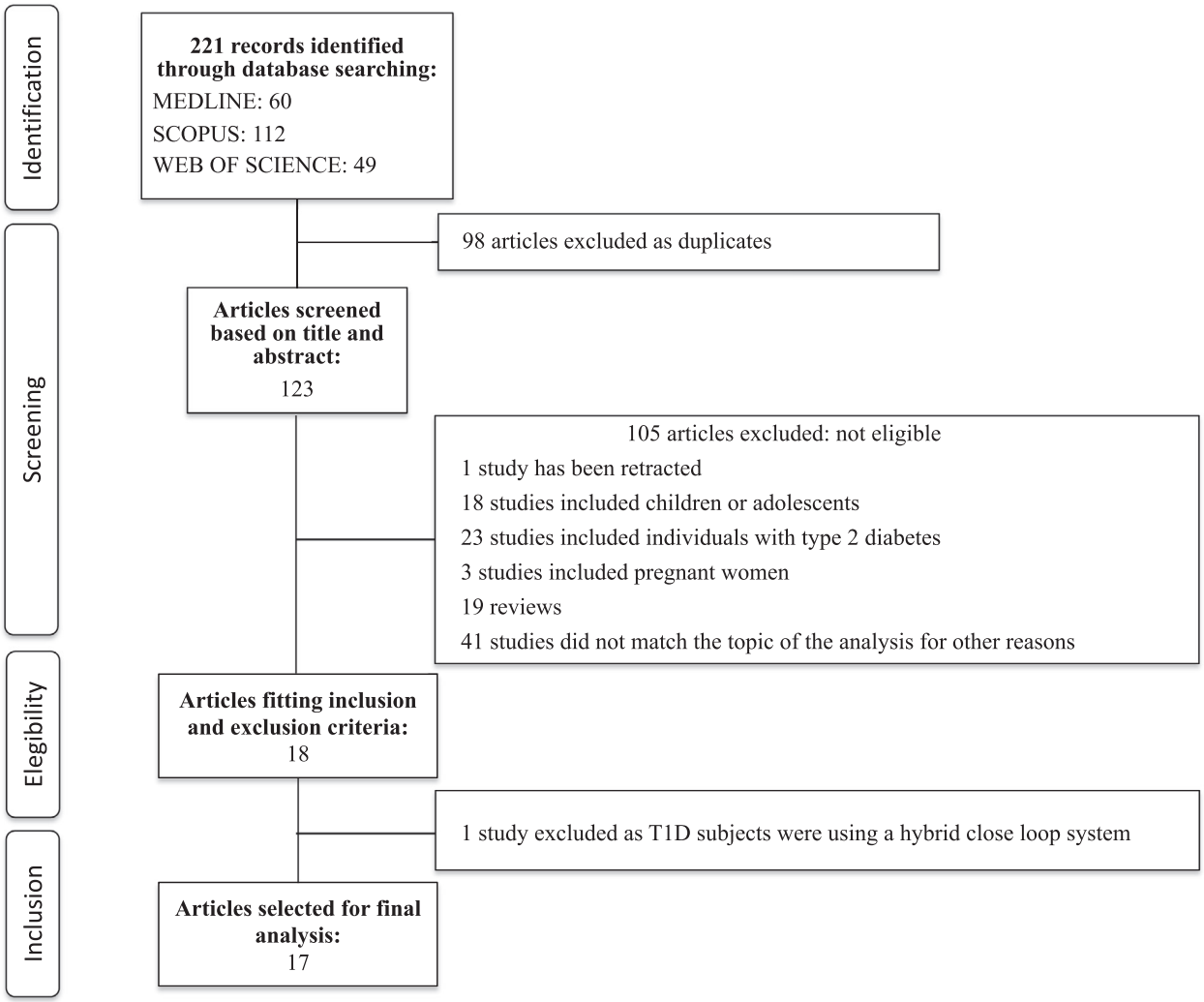



**Fig. 1 – Study selection.**

**Table 1 – Baseline characteristics of subjects enrolled in the 17 studies included in the meta-analysis.**

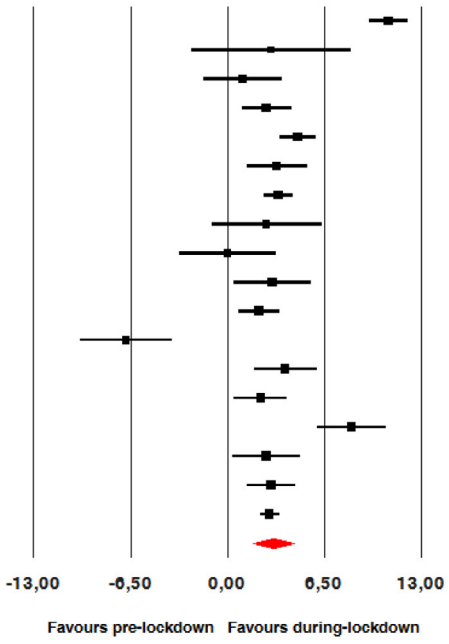
| Study | Country | n. | Type of DM | Observation periods compared in the meta-analysis | Age (years) | DD (years) | HbA1c (%) | % of CGM/FGM | % of MDI/CSII |
|---|---|---|---|---|---|---|---|---|---|
| Bonora BM et al, 2020 [14] | Italy | 20<br>13[†] | 100%<br>T1DM | 1 week before the SARS-CoV-2 outbreak vs the first week after lockdown | 36.9 ± 13.4<br>45.0 ± 12.0 | 15.0 ± 11.1<br>24.6 ± 12.3 | 7.6 ± 1.2<br>7.3 ± 0.6 | 100% FGM | 76% MDI<br>24% CSII |
| Maddaloni E et al, 2020 [15] | Italy | 55 | 91% T1DM<br>5% T2DM<br>4% post-pancreatectomy | 14 days preceding lockdown (24 February to 8 March) and 14 days following lockdown (10–25 March) | 41<br>[IQR 28–49] | 11<br>[IQR 5–23] | – | 100% CGM, not specified | 51% MDI<br>49% CSII |
| Capaldo B et al, 2020 [16] | Italy | 207 | 100% T1DM | 2 weeks before lockdown (January to February) and 2 weeks during lockdown (March to April) | 38.4 ± 12.7 | – | – | 63% FGM<br>37% CGM | 50% MDI<br>50% CSII |
| Fernandez E et al, 2020 [21] | Spain | 307 | 100% T1DM | 14 days before start of lockdown (1–14 March) to the last 14 days of 8 weeks of lockdown (25 April to 9 May) | 45.8 ± 12.6 | 21.1 ± 12.3 | – | 100% FGM | 93% MDI<br>7% CSII |
| Mesa A et al, 2020 [22] | Spain | 92[‡] | 100% T1DM | Before lockdown (23 February to 7 March) to during lockdown (1–14 April) | 42.8 ± 13.9 | 23.1 ± 12.6 | – | 82% FGM<br>18% CGM | 100% MDI |
| Dover AR et al, 2020 [27] | UK | 572 | 100% T1DM | Before lockdown (within 7 days of 11 March) to during lockdown (within 7 days of 14 May) | 39<br>[IQR 31–50) | 18<br>[IQR 9–27) | 7.6<br>[IQR 7.0–8.3) | 100% FGM | 74% MDI<br>26% CSII |
| Cotovad-Bellas L et al, 2020 [23] | Spain | 44 | 100% T1DM | 2 weeks before lockdown (1–14 March) to 2 weeks during lockdown (6–19 April) | 37 ± 18 | – | – | 100% FGM | 100% MDI |
| Caruso I et al, 2020 [17] | Italy | 48 | 100% T1DM | Before lockdown (first 2 weeks of February) to the last 2 weeks before a remote scheduled visit on April | 42.4 ± 15.9 | – | 7.4 ± 1.0 | 100% FGM | 81% MDI<br>19% CSII |
| Aragona M et al, 2020 [18] | Italy | 63 | 100% T1DM | 14 days before start of lockdown (21 February – 6 March) to mid-lockdown (11–25 April) | 44 ± 12 | 22 [IQR 12–32 | 7.2 ± 0.9 | 82% FGM<br>18% CGM | 56% MDI<br>44% CSII |
| Prabhu Navis J et al, 2020 [28] | UK | 269[§] | 100% T1DM | Pre-lockdown period (1–14 February) and mid-lockdown period (1–14 May) | 41.4 ± 12.9 | 23.6 ± 12.9 | 7.3 ± 1.3 | 71% FGM<br>29% CGM | 30% MDI<br>70% CSII |
| Barchetta I et al, 2020 [19] | Italy | 50 | 100% T1DM | Pre-lockdown period (20 January – 3 February) and mid-lockdown period (28 March – 11 April) | 40.7 ± 13.5 | 17.7 ± 9.7 | 7.3 [IQR 6.6–7.8] | 44% CGM<br>56% FGM | 56% MDI<br>44& CSII |
| Di Dalmazi G et al. 2020 [20] | Italy | 76[¶] | 100% T1DM | 20 days before the lockdown (20 February – 10 March) and 20 days starting from 11 to 30 March (during lockdown) | 45.0 [IQR 29.0–58.1] | 22.0 [IQR 14.3–30.8] | 7.3 [IQR 6.6–8.0] | 46% CGM<br>54% FGM | 83% MDI<br>17% CSII |
| Vinals C. et al, 2020 [24] | Spain | 59[‡] | 100% T1DM using SAP | 14 consecutive days before lockdown (23 February – 7 March) to 14 consecutive days during lockdown (1–14 April) | 46.2 ± 13.0 | – | – | 100% CGM | 100% CSII |
| Pla B. et al, 2020 [25] | Spain | 50 | 100% T1DM | 14 days before start of lockdown (1–14 March) to 14 days during lockdown (from 11 april onwards) | 43.4 ± 15.6 | 22.2 ± 12.2 | 7.3 ± 0.8 | 100% FGM | 90% MDI<br>10% CSII |
| Barmpagianni A et al, 2021 [29] | Greece | 46 | 100% T1DM | 15 days immediately before lockdown and lockdown days 16–30 | 38.2 ± 12.9 | 19.5 [IQR 12–28] | | 100% FGM | 100% CSII |
| Moreno-Dominguez O et al, 2020 [26] | Spain | 138 | 100% T1DM | 2 weeks before lockdown (21 February – 5 March) and 2 weeks of lockdown (16–29 March) | 42.5 ± 15.3 | 21.7 ± 13.8 | 7.1 ± 0.9 | 100% FGM | 81% MDI<br>19% CSII |
| Potier L et al, 2020 [30] | France | 1,378 | 100% T1DM | 1 month after lockdown (17 March) and two months before lockdown | 45.6 ± 13.6 | – | 7.4 ± 1.0 | 100% FGM | 84% MDI<br>16% CSII |

DM: diabetes mellitus; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; DD: diabetes duration; CGM: continuous glucose monitoring; FGM: flash glucose monitoring; MDI: multiple daily insulin; CSII: continuous subcutaneous insulin infusion; SAP sensor-augmented pump.

[†] 20 subjects stopped working; 13 subjects continued working; [‡] subjects prone to hypoglycaemia; [§] sensor data comparison between pre-lockdown and lockdown periods available for 223 individuals; [¶] this study included also 30 children (≤12 years) and 24 teenagers (13–17 years).

## A – Time in range (TIR)

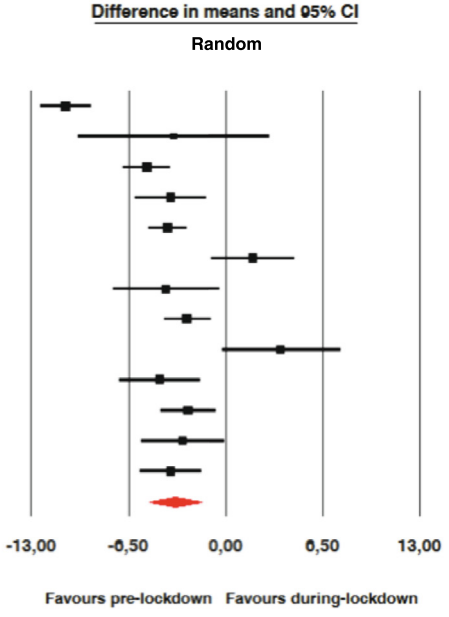
| Study name | Total | Difference in means | Standard error | Lower limit | Upper limit |
|---|---|---|---|---|---|
| Bonora BM et al, 2020 (14) | 20 | 10,800 | 0,655 | 9,517 | 12,083 |
| Bonora BM et al, 2020 (14)* | 13 | 2,900 | 2,746 | -2,482 | 8,282 |
| Maddaloni E et al, 2020 (15) | 55 | 1,000 | 1,341 | -1,627 | 3,627 |
| Capaldo B et al, 2020 (16) | 207 | 2,600 | 0,842 | 0,950 | 4,250 |
| Fernandez E et al, 2020 (21) | 307 | 4,700 | 0,635 | 3,456 | 5,944 |
| Mesa A et al, 2020 (22) | 92 | 3,300 | 1,040 | 1,262 | 5,338 |
| Dover AR et al, 2020 (27) | 572 | 3,400 | 0,504 | 2,413 | 4,387 |
| Cotovad-Bellas et al, 2020 (23) | 44 | 2,600 | 1,885 | -1,095 | 6,295 |
| Caruso I et al, 2020 (17) | 48 | 0,000 | 1,646 | -3,227 | 3,227 |
| Aragona M et al, 2020 (18) | 63 | 3,000 | 1,317 | 0,418 | 5,582 |
| Prabhu Navis et al, 2020 (28) | 223 | 2,100 | 0,694 | 0,740 | 3,460 |
| Barchetta et al, 2020 (19) | 50 | -6,820 | 1,565 | -9,888 | -3,752 |
| Di Dalmazi et al, 2020 (20) | 76 | 3,850 | 1,076 | 1,741 | 5,959 |
| Vinals et al, 2020 (24) | 59 | 2,200 | 0,919 | 0,399 | 4,001 |
| Pla B et al, 2020 (25) | 50 | 8,300 | 1,181 | 5,986 | 10,614 |
| Barmpagianni et al, 2021 (29) | 46 | 2,600 | 1,159 | 0,329 | 4,871 |
| Moreno-Dominguez et al, 2020 (26) | 138 | 2,900 | 0,818 | 1,296 | 4,504 |
| Potier et al, 2020 (30) | 1378 | 2,800 | 0,330 | 2,154 | 3,446 |
| **Total** | 3441 | 3,048 | 0,704 | 1,669 | 4,427 |




**Heterogeneity: $I^2$ 92%**
**Test for overall effect: Z = 4.33, p<0.0001**

## B – Time above range (TAR >180 mg/dL)

| Study name | Total | Difference in means | Standard error | Lower limit | Upper limit |
|---|---|---|---|---|---|
| Bonora BM et al, 2020 (14) | 20 | -10,700 | 0,864 | -12,394 | -9,006 |
| Bonora BM et al, 2020 (14)* | 13 | -3,500 | 3,282 | -9,932 | 2,932 |
| Fernandez E et al, 2020 (21) | 307 | -5,300 | 0,812 | -6,891 | -3,709 |
| Mesa A et al, 2020 (22) | 92 | -3,700 | 1,212 | -6,075 | -1,325 |
| Dover AR et al, 2020 (27) | 572 | -3,900 | 0,665 | -5,203 | -2,597 |
| Caruso I et al, 2020 (17) | 48 | 1,800 | 1,442 | -1,025 | 4,625 |
| Aragona M et al, 2020 (18) | 63 | -4,000 | 1,807 | -7,541 | -0,459 |
| Prabhu Navis et al, 2020 (28) | 223 | -2,600 | 0,811 | -4,190 | -1,010 |
| Barchetta et al, 2020 (19) | 50 | 3,710 | 2,039 | -0,286 | 7,706 |
| Di Dalmazi et al, 2020 (20) | 76 | -4,410 | 1,380 | -7,115 | -1,705 |
| Vinals et al, 2020 (24) | 59 | -2,540 | 0,938 | -4,379 | -0,701 |
| Barmpagianni et al, 2021 (29) | 46 | -2,900 | 1,414 | -5,672 | -0,128 |
| Moreno-Dominguez et al, 2020 (26) | 138 | -3,700 | 1,045 | -5,747 | -1,653 |
| **Total** | 1707 | -3,389 | 0,896 | -5,145 | -1,633 |




**Heterogeneity: $I^2$ 88%**
**Test for overall effect: Z = -3.78, p<0.0001**

**Fig. 2 – Effect of lockdown on blood glucose metrics during lockdown compared to the pre-lockdown period. (A) time-in-range, TIR (70–180 mg/dL); (B) time-above-range, TAR (>180 mg/dL); (C) time-below-range, TBR (<70 mg/dL).**

both clinically and methodologically. Where appropriate, we performed a sensitivity analysis after exclusion of studies with adjunctive specific inclusion criteria. Potential publication bias was analysed using Egger's test and by inspection of the funnel plots. Funnel plots and Egger's test results are provided in the supplementary appendix. Institutional ethical approval was not required because this was a meta-analysis of primary published studies only.

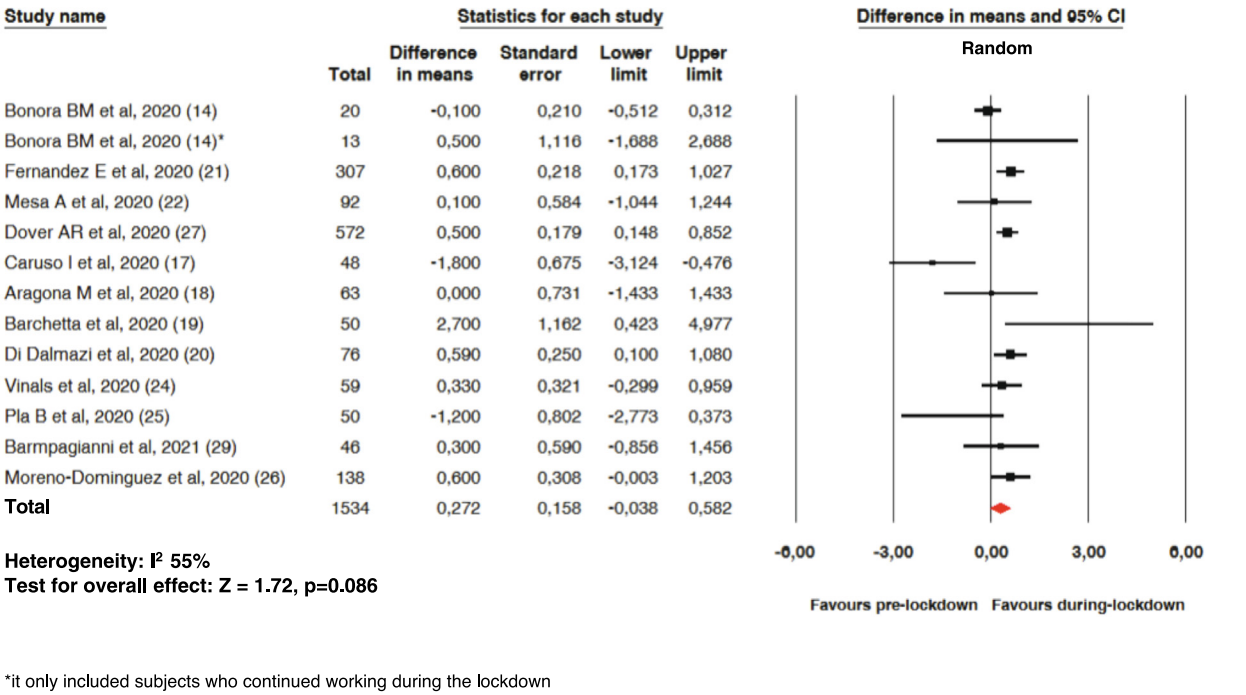



**Fig 2.** *(continued)*

## 3. Results

A total of 221 articles were obtained. After screening titles and abstracts, and after applying all inclusion/exclusion criteria, 18 studies were selected. A further study was excluded because subjects with type 1 diabetes were on a hybrid closed-loop system [13]; thus, a final number of 17 studies was included in this analysis (Fig. 1). Table 1 summarizes the main characteristics of these studies. All of them had retrospective observational design; seven studies have been carried out in Italy [14–20], six in Spain [21–26], two in UK [27,28], and one in Greece [29] and one in France [30]. The sample size ranged from a minimum of 33 and a maximum of 1,378 subjects per study, with a total of 3,441 individuals. One study included few participants with other types of diabetes [15], one study compared subjects who continued vs. those who did not continue working during lockdown [14]. For this study [14], subjects who stopped working and those who continued working were included separately in the analysis. Two studies explicitly included subjects prone to hypoglycaemia [22,24]. Finally, there was no homogeneity between studies across the selected pre- and during lockdown periods (Table 1). Egger's tests and funnel plots inspection did not show significant publication bias (Supplementary Fig. 1 and **Supplementary Table 2**).

### 3.1. *Time in range (TIR)*

TIR was the only outcome available in all studies [14–30]. TIR increased in all but one study [19]. Overall, TIR (difference in means) increased by 3.05% (95% CI 1.67 to 4.43%; $p < 0.0001$) during lockdown, with high heterogeneity ($I^2 = 92\%$; Fig. 2**A**). The statistics did not change after removal of individual studies and even after the removal of the study by Potier et al. (3.03%; 95% CI 1.42 to 4.64%; $p < 0.0001$), in which TIR was not set according to international recommendations [8–10] but was estimated from the mean TIR during the last 90-day period (including the very last 30 days of lockdown) as compared to these 30 lockdown days [30].

### 3.2. *Time above range (TAR)*

TAR, defined as time spent at glucose levels > 180 mg/dL, was available in 12 out of 17 studies [14,17–22,24,26–29] including 1,707 individuals (range: 33 [14] to 572 [27]). TAR decreased in all but two studies [17,19]. Overall, TAR decreased by 3.39% (95% CI −5.14 to −1.63%; $p < 0.0001$), with high heterogeneity ($I^2 = 88\%$; Fig. 2**B**). TAR, defined as time spent at very high glucose (>250 mg/dL), was available in 7 studies [16,20–24,29], corresponding to 831 subjects (from 44 [23] to 307 [21]) and it decreased by 1.96% (95% CI −2.51 to −1.42; $p < 0.0001$), with low heterogeneity ($I^2 = 0\%$; Supplementary Fig. 2**A**). For both outcomes, statistics did not change after the removal of each individual study.

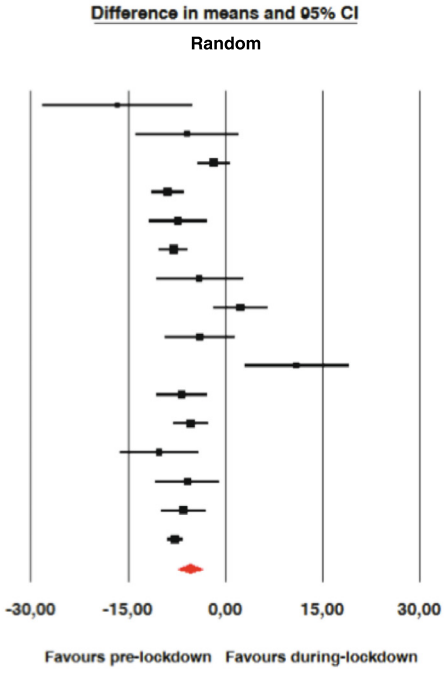
### 3.3. *Time below range (TBR)*

TBR, defined as time spent at glucose levels < 70 mg/dL, was available in 12 studies [14,17–22,24–27,29] including 1,534 individuals (from 33 [14] to 572 [27]). TBR increased in 8 studies

## A – Average blood glucose

| Study name | Total | Difference in means | Standard error | Lower limit | Upper limit |
|---|---|---|---|---|---|
| Bonora BM et al, 2020 (14) | 20 | -16,700 | 5,950 | -28,362 | -5,038 |
| Bonora BM et al, 2020 (14)* | 13 | -5,900 | 4,077 | -13,891 | 2,091 |
| Capaldo B et al, 2020 (16) | 207 | -1,800 | 1,297 | -4,341 | 0,741 |
| Fernandez E et al, 2020 (21) | 307 | -8,900 | 1,274 | -11,396 | -6,404 |
| Mesa A et al, 2020 (22) | 92 | -7,300 | 2,279 | -11,767 | -2,833 |
| Dover AR et al, 2020 (27) | 572 | -8,000 | 1,153 | -10,260 | -5,740 |
| Cotovad-Bellas et al, 2020 (23) | 44 | -4,000 | 3,408 | -10,679 | 2,679 |
| Caruso I et al, 2020 (17) | 48 | 2,300 | 2,175 | -1,962 | 6,562 |
| Aragona M et al, 2020 (18) | 63 | -4,000 | 2,792 | -9,472 | 1,472 |
| Barchetta et al, 2020 (19) | 50 | 11,000 | 4,105 | 2,955 | 19,045 |
| Di Dalmazi et al, 2020 (20) | 76 | -6,720 | 2,016 | -10,671 | -2,769 |
| Vinals et al, 2020 (24) | 59 | -5,390 | 1,383 | -8,100 | -2,680 |
| Pla B et al, 2020 (25) | 50 | -10,260 | 3,083 | -16,302 | -4,218 |
| Barmpagianni et al, 2021 (29) | 46 | -5,900 | 2,529 | -10,857 | -0,943 |
| Moreno-Dominguez et al, 2020 (26) | 138 | -6,500 | 1,808 | -10,043 | -2,957 |
| Potier et al, 2020 (30) | 1378 | -7,800 | 0,633 | -9,042 | -6,558 |
| **Total** | 3163 | -5,438 | 0,954 | -7,309 | -3,568 |

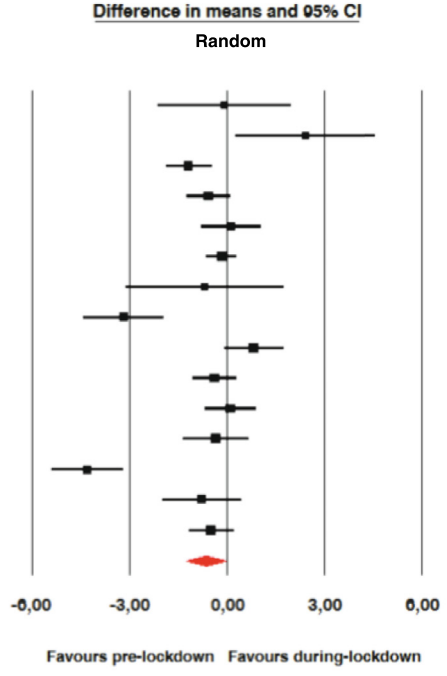
**Heterogeneity: $I^2$ 77%**
**Test for overall effect: Z = -5.60, p<0.0001**




## B – Coefficient of variation (%CV)

| Study name | Total | Difference in means | Standard error | Lower limit | Upper limit |
|---|---|---|---|---|---|
| Bonora BM et al, 2020 (14) | 20 | -0,100 | 1,048 | -2,154 | 1,954 |
| Bonora BM et al, 2020 (14)* | 13 | 2,400 | 1,099 | 0,246 | 4,554 |
| Capaldo B et al, 2020 (16) | 207 | -1,200 | 0,361 | -1,907 | -0,493 |
| Fernandez E et al, 2020 (21) | 307 | -0,600 | 0,344 | -1,274 | 0,074 |
| Mesa A et al, 2020 (22) | 92 | 0,100 | 0,471 | -0,822 | 1,022 |
| Dover AR et al, 2020 (27) | 572 | -0,190 | 0,236 | -0,652 | 0,272 |
| Cotovad-Bellas et al, 2020 (23) | 44 | -0,700 | 1,237 | -3,125 | 1,725 |
| Caruso I et al, 2020 (17) | 48 | -3,200 | 0,634 | -4,443 | -1,957 |
| Aragona M et al, 2020 (18) | 63 | 0,800 | 0,468 | -0,118 | 1,718 |
| Prabhu Navis et al, 2020 (28) | 223 | -0,400 | 0,340 | -1,067 | 0,267 |
| Di Dalmazi et al, 2020 (20) | 76 | 0,080 | 0,401 | -0,706 | 0,866 |
| Vinals et al, 2020 (24) | 59 | -0,360 | 0,509 | -1,357 | 0,637 |
| Pla B et al, 2020 (25) | 50 | -4,310 | 0,568 | -5,424 | -3,196 |
| Barmpagianni et al, 2021 (29) | 46 | -0,800 | 0,624 | -2,024 | 0,424 |
| Moreno-Dominguez et al, 2020 (26) | 138 | -0,500 | 0,348 | -1,182 | 0,182 |
| **Total** | 1958 | -0,655 | 0,300 | -1,242 | -0,067 |

**Heterogeneity: $I^2$ 84%**
**Test for overall effect: Z = -2.18, p=0.029**




*it only included subjects who continued working during the lockdown

**Fig. 3 – Effect of lockdown on (A) average blood glucose and (B) coefficient of variation.**

[19–22,24,26,27,29], decreased in 3 [14,17,25] and did not change in one [18]. In the study by Bonora et al. [14], TBR was reduced in subjects who stopped working and increased in those who continued. Overall, TBR did not change significantly (0.27%, 95% CI −0.04 to 0.58%; $p = 0.086$), with a moderate between-study heterogeneity ($I^2$ = 55%; Fig. 2C). Six studies (785 subjects; range 44 [23] to 307 [21]) reported TBR as time spent at very low glucose levels (<54 mg/dL) [16,20–24]. TBR < 54 mg/dL decreased in 3 studies [16,22,23] and point estimate TBR < 54 mg/dL did not change significantly (−0.14%,

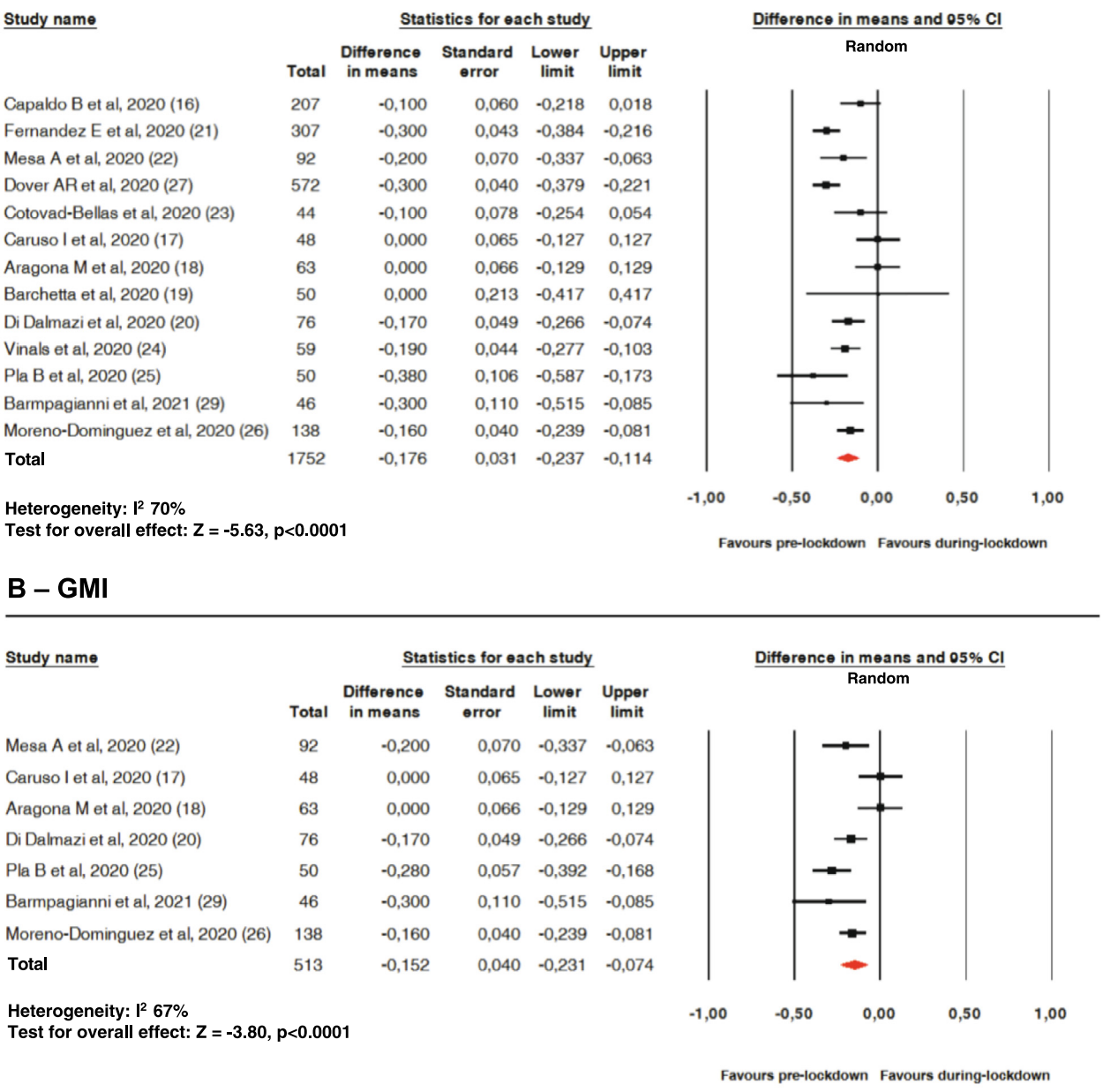



**Fig. 4 – Effect of lockdown on (A) estimated A1c (eA1c) plus glucose management indicator (GMI) pooled; (B) glucose management indicator alone (GMI).**

95% CI −0.53 to 0.26; $p$ = 0.497, $I^2$ = 86%; Supplementary Fig. 2**B**). For TBR < 70 mg/dL, removal of any one of the 3 studies in whom TBR decreased, resulted in a significant effect of lockdown ($p < 0.05$).

### 3.4. *Mean blood glucose and glycaemic variability*

Mean blood glucose (MBG) and glycaemic variability (%CV) were available for 15 and 14 studies including 3,163 and 1,958 individuals, respectively [14,16–27,29,30]; %CV was not reported by Potier et al. [30] MBG and %CV decreased in all but 2 [17,19] and 4 studies [14(only subjects who continue to work), [18,20,22], respectively. Overall, MBG decreased by 5.40 mg/dL (95% CI −7.29 to −3.51 mg/dL; $p < 0.0001$), with high heterogeneity ($I^2$ = 77%; Fig. 3**A**). Coefficient of variation was marginally but statistically modified (−0.66%, 95% CI −1.24 to −0.07%; $p$ = 0.029), with high heterogeneity ($I^2$ = 84%; Fig. 3**B**). For MBG, statistics was

unaffected by the removal of individual studies nor it was after removal of the study by Potier et al. (−5.13 mg/dL; 95% CI −7.30 to −2.96 mg/dL; $p < 0.0001$), in which pre-lockdown MBG was estimated from the MBG of the last 90 days from FGM minus MBG of the last 30 days, assuming the latter to be representative of glycaemic control during lockdown [30].

### 3.5. *Estimated HbA1c (eA1c) and glucose management indicator (GMI)*

Although different calculating methods are used to derive eA1c and GMI [11], in a first analysis we pooled the two variables. Then, a sensitivity analysis was performed including GMI only. Estimated A1c or GMI were reported in all [16–27,29] but 4 studies accounting for a total of 1,752 subjects (from 44 [23] to 572 [27]). The eA1c value decreased in all but 3 studies in which it did not change [17–19]. Overall, eA1c decreased by 0.18% (95% CI −0.24 to −0.11%; $p < 0.0001$), with moderate heterogeneity ($I^2 = 70\%$; Fig. 4**A**). GMI was available in 7 studies [17,18,20,22,25,26,29], including 513 individuals (from 46 [29] to 138 [26]) and decreased in 5 with no change in 2 [17,18]. Overall, GMI decreased by 0.15% (95% CI −0.23 to −0.07%; $p < 0.0001$), with moderate heterogeneity ($I^2 = 67\%$; Fig. 4**B**). For both parameters, the lockdown effects did not substantially differ with the exclusion of any cohort.

### 3.6. *Sensor use*

The percent of sensor use was reported in 10 out of 17 studies accounting for a total of 1,608 subjects. It was found slightly reduced during lockdown as compared to the pre-lockdown period (−0.75%, 95% CI −1.29 to −0.21%; $p = 0.007$), with low heterogeneity ($I^2 = 40\%$). In particular, it was reduced in 7 cohorts [16,18,20–22,26,27], increased in 2 [24,25] and unchanged in the last one [23]. The effect of lockdown did not substantially differ with the exclusion of any cohort with the only exception of the study by Dover et al. [27], the largest one, whose removal made the difference only marginally significant ($p = 0.062$).

## 4. Discussion

This meta-analysis including data from 17 observational studies and a total of 3,441 subjects provides evidence that glucose control modestly though significantly improved during the COVID-19 lockdown period in adults with type 1 diabetes on multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII) using continuous (CGM) or flash glucose monitoring (FGM) systems. This finding may sound at odds with the potential impact of the disruption of regular daily activities, diet, and physical exercise along with a stressful condition the mobility limitation during the lockdown could have exerted. Of interest, only one study has reported a clear-cut worsening of glucose control parameters [19]. Although, the reason for such a difference is not readily apparent, the main trend was for a slight improvement in glycaemic control. As such, our results support and expand those recently published by Silverii et al [31] as other features such as estimated HbA1c and use of the sensor have been included.

The observed improvements in diabetes control were mainly accounted for by an increase in TIR and a concomitant reduction in TAR (both TAR > 180 mg/dL, as well TAR > 250 mg/dL), whereas TBR was only marginally affected, with a trend for an increase in TBR < 70 mg/dL but no changes in TBR < 54 mg/dL. To support this improvement in glycaemic control, a modest thought statistically significant reduction in mean BG as well as in glucose variability were detected. Consistently, also eA1c and GMI improved. These latter parameters are derived from average glucose levels to predict laboratory measured HbA1c [32]. The GMI represents only a slight modification of the eA1c formula, and, therefore, we have pooled the two parameters in our analysis. However, a sensitivity analysis employing just GMI did not yield different results. Of note, all the documented changes in glycaemic control parameters were not due to greater use of the sensors, which was comparable before and during lockdown. Almost all studies included in our meta-analysis collected glucose measurements over at least two weeks immediately before and during lockdown. A 14-day FGM or CGM recording has been previously claimed to provide reliable estimate of glucose metrics [8,32].

Many reasons could account for this result. Diabetes has been recognized as a major risk factor for severe COVID-19 [4,33], which may have increased alertness of people with diabetes and made them to pay more attention to management of their condition [34]. During lockdown, daily care routine has changed deeply, physical activity was found to be reduced [16,35], but more regular patterns of nutrient intake and sleep have been reported [16]. Reduction of physical activity was related to poorer glycaemic control by some [35] but not all investigators [16]. Capaldo et al. [16] showed that reduced physical activity was associated with less glucose variability along with no change in TIR. These discrepant results may not be of a surprise given the variable impact physical activity can have on glucose control in subjects with type 1 diabetes. Although regular exercise can exert a favourable effect it can also represent a challenge in balancing nutrient intake and insulin doses.

Another possible reason for improved glycaemic control could rely in a more regular distribution of daily duties associated with the mobility limitation of the lockdown. In keeping with this hypothesis, Bonora et al. [14] found that, during lockdown, glucose control improved in FGM users who work from home, but not in those who continued their usual working activities. Also, more regular meal patterns, more reproducible mealtimes and increased sleep duration were associated to an increase in TIR [16]. To this regard, it is of interest that at least one study [18] observed a less pronounced “dawn phenomenon” during lockdown, a glycaemic pattern that is supported by the release of counterregulatory stress hormones.

The lack of significant change in TBR deserves some consideration. This may be simply because the rate of hypoglycaemic events was already generally low in most studies. Nevertheless, a significant reduction in TBR was more common for glucose values in the severe hypoglycaemic range

(<54 mg/dL) [16,23], and in subgroups with higher TBR at baseline [14,18], but not in those cohorts claimed at higher risk of severe hypoglycaemia [22,24].

An issue that needs to be taken into consideration in interpreting these results is to which extent the observed changes in glucose control may not simply represent yearly fluctuations. However, by comparing changes occurred during lockdown with the same calendar period in 2019, Dover et al. [27] ruled out that such changes may simply represent a seasonal variation.

Our results, obtained in adult persons with type 1 diabetes, are supported by observational studies performed in children or adolescents with type 1 diabetes using CGM or FGM. In the pediatric age, glucose metrics during lockdown were stable as compared to the pre-lockdown period in some studies [20,36,37] and significantly improved in others [20,38]. These results also sustain the role of technology for management of diabetes that may provide even greater aid during challenging condition as it has been recently reviewed [39]. This is further supported by the results of Longo et al [13] showing that subjects with type 1 diabetes on hybrid closed loop systems with telemedicine support had a significant improvement of metrics of glucose control during the pandemic lockdown.

In summary, the hypothesized deleterious effects of lockdown were not sufficient to disrupt glycaemic control role in type 1 diabetes, or other consequences of the lockdown may have offset such negative effects. It is worth recalling that all these data have been obtained in subjects using CGM or FGM. As such we cannot extend these results to those on traditional SBGM. Telehealth strategies, telemedicine and remote access to sensor data have been proved as effective and efficient tools in the management of type 1 diabetes during COVID-19. These novel ways of delivering care have been explored successfully both in adults [40] as well in children and adolescents with type 1 diabetes [41]. These opportunities might have contributed ensuring glucose control as seen in our meta-analysis, which included studies carried out in developed countries. Consistently, in a recent study, only individuals with type 1 diabetes who attended telemedicine compared to non-attenders had a significant improvement in glucose metrics [42]. On the contrary, higher levels of socioeconomic deprivation (poorer diet, greater stress), which may have also hampered the use of modern technology for glucose monitoring and online supervision, have been reported to be independent predictors for deterioration of glucose control during lockdown [27].

As already mentioned, our results cannot not be generalized to the wider type 1 diabetes population. Recruitments are skewed towards younger individuals recruited within advanced health systems as suggested by many individuals on CSII in many of the cohorts included in our meta-analysis. With respect to this, we could not compare results in subjects on MDI and CSII, even though some studies reported similar results both in adults [16,21] as well as in pediatric individuals [36]. Most of the studies included only people with effective data capture, which may represent a potential selection bias.

On top of that, our meta-analysis has other potential limitations. First, we cannot separate data for CGM users and FGM users nor we could determine the percentage of subjects with a clinically relevant change in eA1c or GMI, for instance an improvement $\geq$ 0.4%. Similarly, we could not estimate how many people had a TIR > 70% or an at least improvement in TIR > 4%, a change reflecting an additional hour per day spent in-range [8]. In the study by Fernández et al. [21], a reduction in eA1c $\geq$ 0.4% and an increase in TIR $\geq$ 5% were observed in 46.6% and 48.2% of subjects, respectively, with 35.8% of subjects with type 1 diabetes achieving such changes. Similar trends, though with numerically different percentages, have been reported in other studies [22,24,26,28], while a deterioration was found to be more common in individuals with higher TIR and lower eA1c at baseline [27]. Finally, most studies selected subjects using both glucose monitoring systems and platforms for remote data sharing, while no solid data documented the extent of life-style changes and the psychological burden. Sometimes, data on physical activity, dietary habits, sleeping patterns, or working routine were provided by online questionnaires and were mainly qualitative and self-reported [30].

In conclusion, our meta-analysis of aggregate data shows that well-controlled people with type 1 diabetes on both MDI and CSII with continuous or flash glucose monitoring did not experience a deterioration in glucose control throughout the COVID-19 lockdown, showing a modest, though statistically significant improvement in many glucose control parameters.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Author contributions

M.G., G.P., and S.D.P. performed literature search, data collection and data analysis. All Authors contributed to interpretation of the findings. M.G. and G.P. wrote the first draft of the paper and all authors provided critical input for intellectual content and approved the final version. All authors had full access to all data of the study, while the corresponding author, S.D.P., had final responsibility for the decision to submit for publication. S.D.P. and G.P. should be considered joint senior author.

## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2021.109066.

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