Prevalence of methylmalonic acidemia among newborns and the clinical-suspected population: a meta-analyse

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ABSTRACT

Importance: Knowing the scale of rare inborn errors is important for screening and resource allocation. Evidence on the prevalence of methylmalonic acidemia (MMA) among newborns and the clinical-suspected population from large-scale screening programs needs to be systematically synthesized.

Objective: To estimate the worldwide prevalence of MMA for newborns and the clinical-suspected population and explore the differences in different regions, periods, and diagnostic technologies.

Data sources: MEDLINE, Embase, CRD, Cochrane Library, Scopus, CINAHL, and PROSPERO. Study Selection: All studies reporting the epidemiology characteristics of MMA were selected.

Data extraction and synthesis: Characteristics of study, subjects, and epidemiology were extracted, random-effect models were used for meta-analyses.

Main outcome and measure: Pooled prevalence of MMA.

Results: This study included 111 studies. The pooled prevalence of MMA worldwide was 1.14 per 100,000 newborns (1516/190,229,777 newborns, 95% CI: 0.99–1.29) and 652.11 per 100,000 clinical-suspected patients (1360/4,805,665 clinical-suspected individuals, CI: 544.14–760.07). Asia and Africa got a higher pooled prevalence of MMA. The prevalence of MMA in newborns increased through the years, while that in the clinical-suspected population decreased. Collecting blood \(\geq 72\) h after birth had a higher pooled prevalence of MMA than collecting during 24–72 h after birth. The combining-use of MS/MS and GC/MS had a higher pooled prevalence than the single-use of MS/MS or GC/MS. Prevalence of cbl C, mut, cbl B, cbl A, isolated MMA, combined MMA and homocystinuria, vitamin B12-responsive MMA was synthesized.

Conclusions and relevance: Prevalence of MMA among newborns was extremely low, but considerably high in the clinical-suspected population, indicating the need for more efficient newborn screening strategies and closer monitoring of the high-risk population for the early signs of MMA. Asia and Africa should attach importance to the high prevalence of MMA. Further diagnostic tests were recommended for the combining-use vs single-use of MS/MS and GC/MS and for collecting blood after 72 h vs during 24–72 h after birth.

Introduction

Methylmalonic acidemia (MMA) is an inborn error and rare disease caused by genetic disorders of methylmalonate \cite{1,2} and cobalamin metabolism \cite{3}. Without early identification and intervention, patients with MMA might suffer from acute metabolic acidosis, multiple organ dysfunction, irreversible developmental retardation, even die at a young age, while a good prognosis can be obtained with simple and timely treatments \cite{4–9}.

Epidemiological information on MMA currently comes from individual screening studies. Newborn screening has been recognized as the most valuable third-tiered measure to prevent birth defects in the world \cite{10}. Due to the nonspecific, heterogeneous manifestations, and their role in causing irreversible but preventable dysfunction, MMA has been one of the primary screening for inherited metabolic disorders (IMDs) in most newborn screening programs. Other than screenings that target newborns, selective screening is also performed for patients with clinically suspected IMDs (“clinical-suspected” population in this study) \cite{11}. These patients are generally characterized

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\textsuperscript{c} Supplemental data for this article can be accessed here.

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by repeated vomiting, slow development, mental retardation, abnormal muscular tone, jaundice, and hepatomegaly, and their laboratory tests often showed metabolic acidosis and positive ketone bodies in urine [11]. Additionally, clinical diagnosis reported in a few studies [12–16] in early years has also provided the prevalence, in which MMA is diagnosed mainly based on the experience of clinicians rather than spectrometry technologies, which was introduced after the 1990s.

The prevalence of MMA in previous literature varied significantly. Auray-Blais C et al. [17] found that the prevalence of MMA was 2.56 in 100,000 newborns in Canada, while Chiju Yang et al. [18] screened the 514,234 newborns in China and found the prevalence to be 17.89 in 100,000 newborns. The variations in reported prevalence could be attributed to many factors, such as geographical regions, ethnics, diagnosis tools and procedures, dried blood spot (DBS) sample collection time, and diagnosis criteria. As for diagnosis technologies, the main techniques are thin-layer chromatography (TLC) [17], gas chromatography/mass spectrometry (GC/MS) [19], and tandem mass spectrometry (MS/MS) [20], and the procedures also varied in different programs, such as the single-use of TLC, MS/MS or GC/MS, as well as the combining-use of MS/MS and GC/MS. Sample collection times are also different among different countries, e.g. China has recommended 72 h~7 days after birth as the time for DBS collection while the American College of Medical Genetics and Genomics (ACMG) has advised collecting DBS at 24~48 h after birth [21]. A comprehensive literature review on MMA prevalence could provide synthesized evidence on the pooled prevalence of MMA, thus enabling the quantification on the scale of the disease and a comprehensive understanding of the variation in the prevalence of each stratum.

This study aims to estimate the pooled prevalence for MMA among newborns and clinical-suspected populations and to identify the differences in prevalence between different regions, periods, and diagnostic technologies through a systematic review and meta-analyses. It may advance the understanding of the epidemiological characteristics and disease burden of MMA in the world. The results of this study may provide a further reference for subsequent improvements on MMA screening programs.

**Methods**

This review was conducted and reported according to The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [22].

**Search strategy and eligibility criteria**

A two-stage search strategy was undertaken (Supplemental Table 1) AQ3. In Stage 1, we identified all articles relevant to screening programs and epidemiology of all types of IMDs in PubMed (MEDLINE), Embase, CRD, Cochrane Library, Scopus, CINAHL, PROSPERO since their establishment; In Stage 2, we identified all articles relevant to epidemiology and screening of MMA in MEDLINE. Supplemental Figure 1 showed the flow diagram of literature searching. To be included, studies had to accurately report the epidemiology data of MMA. Titles/abstracts were screened, and the full texts were retrieved and reviewed by LZ and FH independently. Disagreements were solved by consensus within groups.

**Data collection**

An electronic data extraction form was designed to collect data from eligible studies. For studies that contained the prevalence of MMA for more than one population, region, or screening period, the data in these studies would be extracted for the individual population, region, the screening period.

**Risk of bias assessment**

The risk of bias assessment tool used in this study was developed by Hoy et al. [23], which was designed to evaluate the risk of bias for population-based prevalence studies. The tool is a 10-item checklist, comprising items evaluating selection and nonresponse bias, measurement bias, and the bias related to the analysis. A summary score of 0–3, 4–6, 7–10 indicated low, moderate, high risk, respectively.

**Statistical analysis**

Studies with low and moderate risk of bias were included for further analysis. The prevalence and its 95% confidence interval (CI) were presented as the total number of cases per 100,000 and calculated by the Clopper–Pearson method. If studies provided zero MMA cases, they would still be included but they wouldn’t participate in the synthesis of estimates. Random-effects meta-analysis was used to calculate pooled estimates. Heterogeneity between individual studies was assessed by $I^2$-square ($I^2$) statistics. Subgroup analyses would be conducted if there was at least 1 paper in each subgroup. Grouping factors were as follows: continents, periods (1969–1999, 2000–2010, 2011–2020), diagnosis technologies (main
technologies of TLC, GC/MS, MS/MS were extracted, the usages of them were used for grouping: TLC, the single use of MS/MS, the single use of GC/MS, the combined use of MS/MS and GC/MS, sample collection time (according to the baseline of collecting periods, the sample collecting time was classified into groups of $> 24 \text{h}$, $> 36 \text{h}$, $> 48 \text{h}$, $> 72 \text{h}$, and $>5 \text{ days after birth}$). Meta-regression would be conducted and the study-level characteristics (baseline survey year, publication year, sample size, and risk of bias) were included to explore the source of heterogeneity. Sensitive analysis was carried out to explore the influence of individual studies on the overall estimates. A significance threshold of $p < .05$ was used, two-tail. All analysis was implemented using R 3.6.2 (R Foundation for Statistical Computing) and Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA).

Results

Study characteristic

Table 1 presented the characteristics of included studies. A total of 111 studies (involved 190,229,777 newborns and 4,805,665 clinical-suspected patients) with low and moderate risk of bias were included in this review. The included studies had provided data of 6 continents. The study period was from 1969 to 2019, in which 1969 to 2019 for screening newborns, 1970 to 2019 for screening clinical-suspected population. The sample size of screened population ranged from 26 to 75,100,000, in which 1,127 to 75,100,000 for newborns, and 26 to 596,591 clinical-suspected patients. Extracted data allowed the synthesis of pooled prevalence of the following subtypes: mut (21 studies), cbl A (2 studies), cbl B (4 studies), cbl C (19 studies).

Prevalence of MMA among newborns and clinical-suspected patients

Figure 1 and Figure 2 had shown the meta-analysis of prevalence estimates of MMA for newborns and clinical-suspected populations, respectively. The overall estimate of prevalence of MMA were 1.14 per 100,000 newborns (1,516/190,229,777 newborns, 95% CI: 0.99–1.29, $I^2 = 95.5\%$) and 652.11 per 100,000 clinical-suspected patients (1,360/4,805,665 patients, 95% CI: 544.14–760.07, $I^2 = 95.4\%$). The pooled prevalence among these two populations was significantly different ($p < .001$).

Supplemental Figures 2–4 had exhibited stratified meta-analysis for pooled prevalence among different continents, screening periods, diagnosis technologies, and blood collecting time.

Prevalence stratified by continents

In newborns, it showed that Asia got the highest pooled prevalence of MMA (2.06 per 100,000 newborns, CI: 1.77–2.36, $I^2 = 97.1\%$), followed by North America (1.04 per 100,000, CI: 0.33–1.75, $I^2 = 88.8\%$), Oceania (0.62 per 100,000, CI: 0.14–1.10, $I^2 = 0.0\%$), and Europe (0.33 per 100,000, CI: 0.09–0.57, $I^2 = 28.7\%$), see Supplemental Figure 2.

For the clinical-suspected population, selective screening conducted in Asia (38 studies) was more than that in South America (4 studies), Africa (3 studies), and Europe (1 study). Selective screening reports haven’t been found in North America and Oceania in this study. Stratified meta-analysis showed that Asia got the highest pooled prevalence of MMA (728.99 per 100,000 clinical-suspected patients, CI: 599.19–858.79, $I^2 = 96.0\%$), too, followed by Africa (674.13 per 100,000, CI: 481.62–866.65, $I^2 = 0.0\%$), and South America (674.13 per 100,000, CI: 148.43–478.11, $I^2 = 86.1\%$), see Supplemental Figure 3.

To exclude errors that might be caused by different detection methods, we also compared the results of those studies using the same methods (Supplemental Figure 4). It showed Asia still got the highest pooled prevalence in newborns no matter using what detection methods. Interestingly, in the clinical-suspected population, when adopting the single-use of MS/MS or adopting MS/MS combined GC-MS, the first highest MMA pooled prevalence was in Africa and the second highest prevalence was in Asia.

Prevalence stratified by screening periods

In newborns, the pooled prevalence of MMA has increased from 0.26 per 100,000 newborns between 1969 and 1999 to 1.22 per 100,000 newborns between 2000 and 2010, to 9.38 per 100,000 newborns between 2011 and 2020, see Supplemental Figure 2. While in the clinical-suspected population, the pooled prevalence of MMA has decreased from 1034.06 per 100,000 individuals between 2000 and 2010, to 390.46 per 100,000 individuals between 2011 and 2020, see Supplemental Figure 3.

Prevalence stratified by diagnosis technologies

In newborns, TLC got the highest pooled prevalence of MMA (2.61 per 100,000, CI: 2.13 to 3.10, $I^2 = 0.0\%$), see Supplemental Figure 2. The single use of GC/MS (1.65 per 100,000, CI: −0.13 to 3.43, $I^2 = 95.6\%$) had higher pooled prevalence than the single use of MS/
| Ref | First author (year published) | Country | Screening periods | Sample size | Type of subjects | Dried blood spot collecting time/age | Key testing tools/approaches | Diagnostic criteria (μmol/l) | Risk of bias |
|-----|-------------------------------|---------|------------------|-------------|------------------|-----------------------------------|----------------------------|-------------------------------|-------------|
| [17] | Auray-Blais C et al. (2007) | Canada | 1975–2006 | 2,342,029 | Newborn | 14d of age (in 1973); 21 d old (in 1981) | TLC, GC-MS | NA | 2 |
| [12] | Tangeraas T et al. (2020) | Norway | 2012.3.1–2020.2.29 | 461,369 | Newborn | Average(range): 53 h (40–87 h) | LC-MS/MS; NGS | C3 > 4.75; C3/C2 > 0.25. | 0 |
| [24] | Yang Y et al. (2019) | China | 2014.1–2018.6 | 536,008 | Newborn | Average(range): 4.0 d (3–7), 60 d (61–87 d) | MS/MS; NGS | NA | 2 |
| [13] | Smon A et al. (2017) | Slovenia | 2013–2014 | 10,048 | Newborn | Average(range): 8.5 months (6 to 11 months) | LC-MS/MS; GS-M; MS; NGS | Plasma C3 – high; Urine OA – MMA. | 4 |
| [25] | la Marca G et al. (2008) | Italy | 2002.1–2004.10 | 160,000 | Newborn | 48 and 72 h of life | LC-MS/MS | C3 > 3.3, C3/C0 > 0.13; C3/C4 > 12.5; C3/C4 > 12.5. | 2 |
| [26] | Frazier DM et al. (2006) | USA | 1997.7.28–2005.7.28 | 944,078 | Newborn | Average (range): 5 years | MS/MS | C3 > 4.82; C3 ≥ 9; C3/C2 > 0.15. | 2 |
| [18] | Yang C et al. (2019) | China | 2014.7.14–2018.12.31 | 514,234 | Newborn | 3 and 7 d of life | MS/MS | Reference range: C3 (0.2–4.2); C3/C2 (0.02–0.18); C3/C0 (0.01–0.19). | 1 |
| [27] | Zytkovicz TH et al. (2001) | USA | 1999–2001 | 164,000 | Newborn | 1–3 d after birth. | MS/MS | NA | 0 |
| [28] | Mohamed S et al. (2020) | Saudi Arabia | 2012.1–2017.12 | 56,632 | Newborn | 24 h after birth | MS/MS | C3 > 10; C3/C2 > 0.4. | 4 |
| [29] | Deng K et al. (2020) | Mainland China | 2016.1–2017.12 | 461,500 | Newborn | Average (range): 4.0 d (3–7) | MS/MS, NGS | Reference range: C3 (0.2–4.2); C3/C2 (0.04–0.22). | 1 |
| [30] | Lin Y et al. (2019) | China | 2014.4–2018.12.31 | 514,234 | Newborn | 3 and 7 d of life | MS/MS | Reference range: C3 (0.3–4.5); C3/C0 (0.02–0.2); C3/C2 (0.01–0.2). | 1 |
| [31] | Shibata N et al. (2018) | Japan | 2001–2014 | 13,900,000 | Newborn | 48–72 h after birth in Japan, South Korea and Taiwan, and 36–72 h after birth in Germany. | MS/MS | C3 < 3.84. | 1 |
| [32] | Shibata N et al. (2018) | Korea | 2000–2015 | 34,400,000 | Newborn | 48–72 h after birth | MS/MS | C3 < 3.84. | 1 |
| [33] | Shibata N et al. (2018) | Germany | 2002–2015 | 75,100,000 | Newborn | 36–72 h after birth | MS/MS | C3 < 3.84. | 1 |
| [34] | Alfadhel M et al. (2017) | Saudi Arabia | 2005.8.1–2012.12.31 | 775,000 | Newborn | After 24 h of age | MS/MS | C3 > 6.5. | 1 |
| [35] | Hassan FA et al. (2016) | Egypt | 2008.1–2009.11 | 25,276 | Newborn | NA | MS/MS | Reference range: C3 (0.2–4.3); C3/C2 (0.02–0.17). | 1 |
| [36] | Kneissler I et al. (2015) | Lebanon | 2007–2013 | 126,000 | Newborn | NA | MS/MS | C3 < 3.84. | 1 |
| [37] | Scalamiero E et al. (2015) | Italy | 2007.5–2014.9.30 | 45,466 | Newborn | 48–72 h after birth | MS/MS | C3 < 3.84. | 1 |
| [38] | Lim JS et al. (2014) | Japan | 2006.6–2014.4 | 177,267 | Newborn | First sample at 24–72 h, 2nd at 4 weeks of life and 3rd at 4 weeks of life. | MS/MS | C3 < 3.84. | 1 |
| [39] | Barends M et al. (2014) | England | 2002.2–2014.1 | 847,418 | Newborn | 48–72 h of age | MS/MS | C3 < 3.8, C3/C2 < 0.18. | 1 |
| [40] | Lund AM et al. (2012) | Denmark | 2002.2–2011.3.31 | 504,049 | Newborn | Median age was 2.5 d. | MS/MS | C3 > 6.0; C3/C2 > 0.25. | 1 |
| [41] | Lindner M et al. (2011) | Germany | 1999.1.1–2009.6.30 | 1,084,195 | Newborn | Between day of life three to five before 2002 and between 36 and 72 h thereafter. | MS/MS | C3 < 3.84. | 1 |
| [42] | Couce ML et al. (2011) | Spain | 2000.7.1–2010.7.1 | 210,165 | Newborn | Before 2002: between the 5th MS/MS and 8th days. Since 2002: 3rd day of life. | MS/MS | C3 < 3.84. | 1 |
Table 1. Continued.

| Ref   | First author (year published) | Country          | Screening periods               | Sample size   | Type of subjects | Dried blood spot collecting time/age | Key testing tools/approaches | Diagnostic criteria (μmol/l) | Risk of bias |
|-------|-------------------------------|------------------|---------------------------------|---------------|------------------|-------------------------------------|-------------------------------|-----------------------------|--------------|
| [46]  | Lee HC et al. (2011)          | China            | 2005–2009 before 2009 (2004–2008) | 177,000       | NA               | NA                                  | Between days 3 and 6 of life | MS/MS, GC-MS                | NA           |
| [47]  | Vilarinho L et al. (2010)     | Portugal         | before 2009 (2004–2008)         | 316,243       | Newborn          | NA                                  | NA                            | MS/MS, GC-MS                | NA           |
| [48]  | Niu DM et al. (2010)          | China            | 2000.3–2009.6                   | 1,321,123     | Newborn          | 24 h after the first feeding or MS/MS | 48 h (but not later than 72 h) | C3, C3/C2, C3/C0            | NA           |
| [49]  | Louskas YL et al. (2010)      | Greece           | 2007.7–2009.12                  | 45,000        | Infants born in Athens, Greece | 72 h of life | MS/MS, GC-MS | C3 > 7.00, C3/C2 > 0.31. | 2            |
| [50]  | Kasper DC et al. (2010)       | Austria          | 2002.4–2009.12                  | 622,489       | Newborn          | 36 and 72 h of life                 | MS/MS, GC-MS | C3 > 6.0, C3/C2 > 0.3 | 4            |
| [51]  | Moammar H et al. (2010)       | Saudi Arabia     | 1983.11–2008.12.31              | 165,530       | Newborn          | 5 and 8 d of age                    | MS/MS, GC-MS | NA               | 3            |
| [52]  | Walter JH et al. (2009)       | England          | before 2009.8.11                | 24,983        | Newborn          | 3 of age                            | MS/MS, GC-MS | NA               | 3            |
| [53]  | CDC (2006)                    | USA              | 2001–2006                       | 2,174,313     | Newborn          | 3 of age                            | MS/MS, GC-MS | NA               | 3            |
| [54]  | Loukas YL et al. (2010)       | Greece           | 2007.8–2009.12                  | 7,315         | Babies 21 d after their birth Babies 21 d after their birth | MS/MS, GC-MS | C3 > 7.00, C3/C2 > 0.31. | 2            |
| [55]  | Schulze A et al. (2003)       | Germany          | 1998.4–2011.9                   | 250,000       | Newborn          | 3rd and 7th day of life             | C3 > 6.0, C3/C2 > 0.31. | 2            |
| [56]  | Hoffmann GF et al. (2004)     | Germany          | NA                             | 382,247       | Newborn          | 5th day                             | MS/MS, GC-MS | NA               | 3            |
| [57]  | Naylor EW et al. (1999)       | United Kingdom   | 1997.11–1999.30                 | 687,630       | Newborn          | 48 h of age, and usually on day 3 of life | MS/MS, GC-MS | NA               | 3            |
| [58]  | Guo K et al. (2018)           | China            | 2015.1–2015.12                  | 48,297        | Newborn          | Infants born in Jining, China, between January 2015 and December 2015 | Between 3rd and 10th day of life | NA | 2          |
| [59]  | Applegarth DA et al. (2002)   | Canada           | 1997.4–2001.7                   | 102,200       | Newborn          | 5th or sixth day of life            | MS/MS, GC-MS | NA               | 3            |
| [60]  | Applegarth DA et al. (2000)   | Korea            | before 1999                     | 16,246        | Newborn          | 48h of age or more, and usually on day 3 of life | MS/MS, GC-MS | NA               | 3            |
| [61]  | Preeti Sharma et al. (2018)   | India            | 2013.5–2014.12                  | 371,942       | Newborn          | 37.16                               | MS/MS, GC-MS | NA               | 3            |
| [62]  | Al Hosani H et al. (2013)     | the United Arab Emirates | 1979–1996 | 137,120 | Newborn          | 48h of age or more, and usually on day 3 of life | MS/MS, GC-MS | NA               | 3            |
| [63]  | C Cantú-Reyna et al. (2016)   | Mexico           | 2012.11–2014.8.9                | 10,000        | Newborn          | Birth before 48h of life            | MS/MS, GC-MS | NA               | 2            |
| [64]  | Chong SC et al. (2017)        | China            | 2015.3–2017.3                   | 30,448        | Newborn          | Birth before 48h of life            | MS/MS, GC-MS | NA               | 2            |
| [65]  | Shi XT et al. (2012)          | Mainland China   | 2004–2007                       | 317,942       | Newborn          | 37.16                               | MS/MS, GC-MS | NA               | 2            |
| [66]  | Park KJ et al. (2016)         | Korea            | 2013.5–2014.12                  | 93,165        | Newborn          | 37.16                               | MS/MS, GC-MS | NA               | 2            |
| [67]  | Applegarth DA et al. (2000)   | Canada           | 1997–1998                       | 1,105         | Newborn          | 2 or 3, and usually on day 3 of life | MS/MS, GC-MS | NA               | 2            |
| [68]  | Al Bu Ali WH et al. (2011)    | Saudi Arabia     | 2006.4–2009                     | 37,168        | Newborn          | 37.16                               | MS/MS, GC-MS | NA               | 2            |
| [69]  | Yamaguchi S (2008)            | Japan            | 1997–2007                       | 606,380       | Newborn          | 37.16                               | MS/MS, GC-MS | NA               | 2            |
| [70]  | Peetee Sharma et al. (2018)   | India            | 2012.10–2015.11                 | 70,590        | Newborn          | 37.16                               | MS/MS, GC-MS | NA               | 2            |
| [71]  | Wilson C et al. (2008)        | Australia        | 2004.1–2006                     | 270,000       | Newborn          | 37.16                               | MS/MS, GC-MS | NA               | 3            |
| [72]  | Huang XW et al. (2011)        | China            | 2009.1–2010.9                   | 129,415       | Newborn          | 72 h after birth and 8 breastfeeds. | MS/MS, GC-MS | NA               | 3            |
| Ref | First author (year published) | Country | Screening periods | Sample size | Type of subjects | Dried blood spot collecting time/age | Key testing tools/approaches | Diagnostic criteria (μmol/l) | Risk of bias |
|-----|-------------------------------|---------|------------------|-------------|------------------|-------------------------------------|----------------------------|-----------------------------|--------------|
| [78] | WANG LW et al. (2019) | China | 2012.12–2018.12 | 820,337 | Newborn | Newborns in Henan province who were fully breast-fed 72 h after birth. | MS/MS | Reference range: C3 (0.32–4.1), C3/C2 (0.04–0.23), C3/C0 (0.01–0.16). | 3 |
| [79] | Hong F et al. (2017) | China | 2009.1–2016.12 | 1,861,262 | Newborn | 72 h after birth and enough breastfeeds. | MS/MS | NA | 3 |
| [80] | Zhang R et al. (2021) | China | 2014.1–2019.12 | 146,152 | Newborn | An average age of 7.25 d at birth. | MS/MS | C3: 0.35–4.00; C3/C2: 0.03–0.18; C3/Met: 0.02–0.25; C3/C0: 0.02–0.22. | 3 |
| [81] | Ao Zhenzhen et al. (2020) | China | 2013.6–2019.6 | 20,000 | Newborn | | MS/MS | NA | 3 |
| [82] | Xu K et al. (2001) | China | 1999.2–2000.8 | 393 | Subjects suspected of having IEM. | | NA | 3 |
| [83] | Hori D et al. (2005) | Japan | 1995–2002 | 4,653 | Subjects suspected of having IEM. | | NA | 3 |
| [84] | Hori D et al. (2005) | Asia | 1995–2002 | 1,369 | Subjects suspected of having IEM. | | NA | 3 |
| [85] | Han LS et al. (2007) | China | 2002–2006 | 3,070 | Subjects suspected of having IEM. | | NA | 3 |
| [86] | Marquez-Caraveo ME et al. (2020) | Mexico | 2017.6–2019.7 | 51 | Subjects suspected of having IEM. | | NA | 3 |
| [87] | Wajner M et al. (2018) | Brazil | 2017.6–2018.12 | 21,800 | Subjects suspected of having IEM. | | GC-MS; LC-MS/MS; reverse phase HPLC. | NA | 3 |
| [88] | Altimimi HA et al. (2019) | Iraq | 2017.4–2018.41 | 112 | Subjects suspected of having IEM. | | NA | 3 |
| [89] | Vargas CR et al. (2018) | Brazil | 2013.6–2019.6 | 20,000 | Subjects suspected of having IEM. | | NA | 3 |
| [90] | ICNTR Task Force (2017) | India | before 2017 | 851 | Subjects suspected of having IEM. | | NA | 3 |
| [91] | Shibata N et al. (2018) | Japan | 2000–2015 | 30,625 | Subjects suspected of having IEM. | | NA | 3 |
| [92] | Shibata N et al. (2018) | Vietnam | 2000–2015 | 3,054 | Subjects suspected of having IEM. | | NA | 3 |
| [93] | Shibata N et al. (2018) | China | 2000–2015 | 2,105 | Subjects suspected of having IEM. | | NA | 3 |
| [94] | Wang H et al. (2017) | China | 2013.6–2015.10 | 183 | Subjects suspected of having IEM. | | GC-MS/MS. | Increased level of C3 and C3/C2; elevated level of methylmalonic acid and methyl citrate. | 3 |
| [95] | Hampe MH et al. (2016) | India | 2013.7–2016.1 | 23,140 | Subjects suspected of having IEM. | | GC-MS; LC-MS/MS; reverse phase HPLC. | NA | 3 |
| [96] | Dogan E et al. (2017) | Turkey | 2010.1–2016.12 | 4,800 | Subjects suspected of having IEM. | | NA | 3 |
| [97] | Hassan FA et al. (2016) | Egypt | 2008.1–2015.1 | 3,900 | Subjects suspected of having IEM. | | NA | 3 |
| [98] | Kiykim E et al. (2016) | Turkey | 2009.1–2014.2 | 778 | Subjects suspected of having IEM. | | NA | 3 |
| [99] | Han L et al. (2014) | China | 2002.2–2012.6 | 18,303 | Subjects suspected of having IEM. | | NA | 3 |
| [100] | Jiang M et al. (2015) | China | 2009.1–2012.3 | 16,075 | Subjects suspected of having IEM. | | NA | 3 |
| [101] | Shawky RM et al. (2015) | Egypt | NA | 40 | Subjects suspected of having IEM. | | NA | 3 |
| [102] | Selim LA et al. (2014) | Egypt | 2008.6–2013.6 | 3,380 | Subjects suspected of having IEM. | | NA | 3 |

**Table 1. Continued.**
Table 1. Continued.

| Ref | First author (year published) | Country | Screening periods | Sample size | Type of subjects | Dried blood spot collecting time/age | Key testing tools/approaches | Diagnostic criteria (μmol/l) | Risk of bias |
|-----|--------------------------------|---------|-------------------|-------------|-----------------|------------------------------------|----------------------------|-----------------------------|--------------|
| [97] | Golbahar J et al. (2013) | Bahrain | 2008.1.1–2011.12.31 | 1,986 | Subjects suspected of having IEM. | NA | MS/MS | High C3; High urinary methyliminonic acid; Reversed phase chromatography; Ion-exchange chromatography; GC-MS. | 2 |
| [98] | Karam PE et al. (2013) | Lebanon | 1998–2010 | 2,921 | Subjects suspected of having IEM. | NA | Reversed phase chromatography; Ion-exchange chromatography; GC-MS. | Homocystine + Methylmalonic, methylcitric. | 2 |
| [99] | Tu W et al. (2012) | China | 2009.1.1–2009.8.31 | 724 | Subjects suspected of having IEM. | NA | MS/MS | C3 < 5.0; C4DC < 0.60; C3/C6 < 2.0; C3/C2 < 0.3; C3 (0.47–4.33). | 2 |
| [100] | Huang X et al. (2012) | China | 2008–2011 | 11,060 | Subjects suspected of having IEM. | NA | MS/MS | C3 (0.47–4.33). | 2 |
| [101] | Al Riyami S et al. (2012) | The Sultanate of Oman | 1998.5–2008.7 | 1,100 | Subjects suspected of having IEM. | NA | MS/MS | NA | 2 |
| [102] | Tu WJ et al. (2010) | China | 2008.10.1–2009.9.30 | 26 | Subjects suspected of having IEM. | NA | LC-MS/MS | C3 < 5.8; C3/C2 < 0.32; C3/C16 < 2.2. | 2 |
| [103] | Nagaraja D et al. (2010) | India | 2007–2009 | 3,550 | Subjects suspected of having IEM. | NA | MS/MS | C4DC (0.00–2.6); C3 (0.32–5.81); C3/C0 (0.00–0.53); C3/C2 (0.02–0.36) | 2 |
| [104] | Wajner M et al. (2009) | Brazil | 1994.1–2008.7 | 6,866 | Subjects suspected of having IEM. | NA | GC-MS | NA | 2 |
| [105] | Song Y et al. (2008) | China | before 2007 | 618 | Subjects suspected of having IEM. | NA | GC-MS | NA | 2 |
| [106] | Yang Y et al. (2008) | China | 1998.6–2007.5 | 9,566 | Subjects suspected of having IEM. | NA | GC-MS, MS/MS, fluorescence polarization immunoassay. | GC-MS, MS/MS, enzyme analysis, genetic analysis. | 2 |
| [107] | Abdel-Hamid M et al. (2007) | Kuwait | 2004.5–2006.3 | 362 | Subjects suspected of having IEM. | NA | MS/MS | NA | 2 |
| [108] | Joshi SN et al. (2007) | The Sultanate of Oman | 1998.6–2005.5 | 166 | Subjects suspected of having IEM. | NA | MS/MS | NA | 2 |
| [109] | Tan IK et al. (2006) | Singapore | 1992–2005 | 3,656 | Subjects suspected of having IEM. | NA | MS/MS | NA | 2 |
| [110] | Yoon HR et al. (2005) | South Korea | 2001.4–2004.3 | 6,795 | Subjects suspected of having IEM. | NA | Between 1 month and 18 years of age | GC-MS, HPLC. | 2 |
| [111] | Shigematsu Y et al. (2002) | Japan | before 2001 | 164 | Subjects suspected of having IEM. | NA | MS/MS | C3/C2 > 0.25 | 2 |
| [112] | Wajner M et al. (2002) | Brazil | 1994.1–2001.7 | 1,926 | Subjects suspected of having IEM. | NA | GC-MS | NA | 2 |
| [113] | Chace DH et al. (2001) | United States and Canada | 1996.5.1–2000.11.30 | 7,038 | Subjects suspected of having IEM. | NA | MS/MS | C3, C3/C2 | 2 |
| [114] | Machill G et al. (1994) | Germany | 1970–1994 | ~130,000 | Subjects suspected of having IEM. | NA | GC-MS, HPLC. | NA | 3 |
| [115] | Lehner W et al. (1994) | Germany | 1973–1990 | ~40,000 | Subjects suspected of having IEM. | NA | GC-MS | NA | 3 |
| [116] | Lehner W et al. (1984) | Germany | 1975–1981 | ~9,000 | Subjects suspected of having IEM. | NA | GC-MS | NA | 3 |
| [117] | Chalmers RA et al. (1980) | England | before 1980 | 695 | Subjects suspected of having IEM. | NA | GC-MS, TLC. | NA | 2 |
| [118] | Bower A et al. (2019) | France | 2010.1.1–2014.12.31 | 11,301 | Subjects suspected of having IEM. | NA | MS/MS, GC-MS. | NA | 2 |
| [119] | Haferz A et al. (2020) | Pakistan | 2015.4–2018.3 | 805 | Subjects suspected of having IEM. | NA | Ion Exchange Chromatography; GC-MS. | NA | 2 |
| [120] | AlObaidy H et al. (2013) | Libya | 2001.1–2012.12 | 19,938 | Subjects suspected of having IEM. | Between 24h | MS/MS | NA | 2 |

(continued)
| Ref | First author (year published) | Country | Screening periods | Sample size | Type of subjects | Dried blood spot collecting time/age | Key testing tools/approaches | Diagnostic criteria (μmol/l) | Risk of bias |
|-----|-------------------------------|---------|------------------|-------------|------------------|-------------------------------------|-----------------------------|-----------------------------|-------------|
| [118] | Gündüz M et al. (2015) | Turkey | 2010.1-2013.6 | 2,994 | Subjects suspected of having IEM. | NA | Ion-exchange chromatography; GC-MS. | NA | 2 |
| [119] | Cheema HA et al. (2016) | Pakistan | 2011.1-2014.10 | 239 | Subjects suspected of having IEM. | NA | MS/MS, GC-MS. | NA | 2 |
| [120] | Lin SX et al. (2019) | China | 2012.2-2016.12 | 15,851 | Subjects suspected of having IEM. | NA | GC-MS | NA | 2 |
| [121] | Gu XF et al. (2011) | China | 2002.11-2003.6 | 104 | Subjects suspected of having IEM. | NA | MS/MS | NA | 2 |
| [122] | Xu FL et al. (2012) | China | 2008.6-2011.8 | 287 | Subjects suspected of having IEM. | NA | GC-MS | NA | 2 |
| [123] | Luo XP et al. (2003) | China | 2001.4-2002.10 | 352 | Subjects suspected of having IEM. | NA | GC-MS | NA | 2 |
| [124] | Xie LJ et al. (2008) | China | 2003.6.1-2006.9.30 | 132 | Subjects suspected of having IEM. | NA | MS/MS, GC-MS. | C3 < 4.00; C3/C0 < 0.20; C3/C2 < 0.35. | 2 |
| [125] | Han Lian-shu et al. (2006) | China | ? 2003-2006 | 2,566 | Subjects suspected of having IEM. | NA | MS/MS, GC-MS, Enzyme analysis, gene analysis. | C3, C3/C2, C3/C0. | 2 |
| [12] | Tangeras T et al. (2020) | Norway | 2002-2012 | 596,591 | Subjects suspected of having IEM. | NA | NA | NA | 5 |
| [13] | Smon A et al. (2017) | Slovenia | 1999-2013 | 293,897 | Newborn | NA | NA | NA | 5 |
| [14] | Wilcken B et al. (2009) | Australia | 1994-1998 | 1,017,800 | Unscrened infants. | NA | NA | NA | 4 |
| [14] | Wilcken B et al. (2009) | Australia | 1998-2002 | 533,400 | Unscrened infants. | NA | NA | NA | 5 |
| [15] | Wilcken B et al. (2003) | Australia | 1974-1979 | NA | Subjects suspected of having IEM. | NA | GC | Clinical diagnosis | 5 |
| [15] | Wilcken B et al. (2003) | Australia | 1978-1982 | NA | Subjects suspected of having IEM. | NA | NA | Clinical diagnosis | 5 |
| [15] | Wilcken B et al. (2003) | Australia | 1982-1986 | NA | Subjects suspected of having IEM. | NA | NA | Clinical diagnosis | 5 |
| [15] | Wilcken B et al. (2003) | Australia | 1986-1990 | NA | Subjects suspected of having IEM. | NA | NA | Clinical diagnosis | 5 |
| [15] | Wilcken B et al. (2003) | Australia | 1990-1994 | NA | Subjects suspected of having IEM. | NA | NA | Clinical diagnosis | 5 |
| [15] | Wilcken B et al. (2003) | Australia | 1994-1998 | NA | Subjects suspected of having IEM. | NA | NA | Clinical diagnosis | 5 |
| [16] | Wilson C et al. (2008) | New Zealand | 2004.1-2006 | 175,000 | Newborn | NA | NA | NA | 5 |
MS (1.25 per 100,000, CI: 1.01 to 1.48, \(I^2 = 96.8\%\)). Compared with the single use of MS/MS or GC/MS, the combining use of MS/MS and GC/MS (1.91 per 100,000, CI: 1.28 to 2.55, \(I^2 = 92.5\%\)) had higher pooled prevalence.

In clinical-suspected patients, the combining use of MS/MS and GC/MS (1429.71 per 100,000 clinical-suspected patients, CI: 1071.43–1787.98, \(I^2 = 97.4\%\)) had the highest pooled prevalence compared with the single use of MS/MS or GC/MS, see Supplemental Figure 3. The single use of GC/MS (596.43 per 100,000, CI: 426.38–766.48, \(I^2 = 89.4\%\)) had higher pooled prevalence than the single use of MS/MS (306.30 per 100,000, CI: 199.94–412.65, \(I^2 = 88.7\%\)).

Prevalence stratified by DBS collecting time
For the variety of dried blood spots (DBS) collecting age among different programs, there were 33 studies that could support this subgroup analyses. Supplemental Figure 2 showed collecting DBS \(\geq 72\) h after birth had the highest pooled prevalence of MMA (5.46 per 100,000 newborns, CI: 3.68 to 7.14, \(I^2 = 96.5\%\)).

Prevalence of subtypes of MMA
Overall estimates of the prevalence of MMA due to methylmalonyl-CoA mutase deficiency (mut type), MMA due to the defect of adenosylcobalamin (cbl) metabolism (cbl A, cbl B, cbl D, cbl C, cbl F, cbl J), isolated MMA (mut, cbl A, cbl B, cbl D-variant 2), combined MMA and homocystinuria (cbl C, cbl D, cbl F, cbl J), vitamin B12-responsive MMA (cbl A, cbl B), vitamin B12-unresponsive MMA (mut type) could be observed from the reported studies and they were summarized in Supplemental Figure 5. It showed the pooled prevalence of cbl C (2.35 per 100,000 newborns, CI: 1.45–2.35, \(I^2 = 93.0\%\)) was the highest among that of other subtypes, followed by mut (0.98 per 100,000 newborns, CI: 0.58–1.39, \(I^2 = 88.7\%\)).
69.0%), cbl B (0.41 per 100,000 newborns, CI: −0.50 to 1.32, $I^2 = 63.1\%$), and cbl A (0.22 per 100,000 newborns, CI: −0.33 to 0.77, $I^2 = 0.0\%$). And the pooled prevalence of complete mutase deficiency (mut 0: 0.21 per 100,000 newborns, CI: 0.14 to 0.57, $I^2 = 0.0\%$) was higher than that of partial mutase deficiency (mut−: 0.21 per 100,000 newborns, CI: 0.14 to 0.57, $I^2 = 0.0\%$).

As for pooled prevalence of subtypes for biochemical phenotypes, combined MMA and homocystinuria got the highest estimates (1.70 per 100,000 newborns), followed by MMA due to the defect of adenosylcobalamin (cbl) metabolism (1.28 per 100,000 newborns, CI: 0.81 to 1.75, $I^2 = 89.0\%$) and isolated MMA (0.99 per 100,000 newborns, CI: 0.67 to 1.30, $I^2 = 60.2\%$). As for clinical phenotypes, vitamin B12–unresponsive MMA (0.98 per 100,000 newborns, CI: 0.58 to 1.39, $I^2 = 69.0\%$) had a higher pooled prevalence than vitamin B12–responsive MMA (0.30 per 100,000 newborns, CI: 0.07 to 0.52, $I^2 = 38.8\%$).

**Heterogeneity analysis**

Sensitive analysis for each subtype showed that individual studies have minor differences to meta-analyses estimates and they could be considered robust because no individual study had affected most of the pooled estimates by more than 5.0%. Meta-regression results showed that baseline survey year ($p < 0.001$), publish year ($p < 0.001$), sample size ($p < 0.001$), and risk of bias ($p < 0.001$) might account for the high heterogeneity.

**Discussion**

This review had comprehensively reported the difference and characteristics of the prevalence of MMA among newborns and clinical-suspected populations. To our knowledge, nearly none of the systematic reviews had reported them previously [126–128]. In this review, the synthesis estimate of the prevalence of MMA among the newborn population was 1.14 per 100,000, which was consistent with Almäsi T et al. [126], in which the pooled prevalence was below 2 cases per 100,000 for 39 studies.

The prevalence of MMA among clinical-suspected populations was significantly higher than that among the newborn population irrespective of regions, years, and diagnostic technologies. The inherited reason should be the missing of early identification. MMA is a
monogenic inherited disease, once missing the identification in the early years, patients will get a high possibility of developing into symptomatic [7]. Reasons for missing the early identification should be carefully investigated, it's might be multiple, maybe the small coverage of newborn screening for MMA in the early years or the high false-negative rate of MMA identification. Further studies can be carried out to find more efficient strategies for early identification [24].

It's shown that Asia and Africa got a relatively higher pooled prevalence than other continents in both populations. In addition, Africa had a very high MMA prevalence in the clinical-suspected population while the prevalence in newborns remains unclear, indicating Africa should pay attention to the early screening and prevention of MMA. Besides, these results may reflect the high rate of consanguineous marriage in Asia and Africa [129,130], and further studies investigating the associations of the occurrence of MMA with consanguineous marriage rate are necessary.

The prevalence of MMA among newborns had been obviously increasing from 0.26 per 100,000 between 1969 and 1999 to 1.22 per 100,000 between 2000 and 2010 and to 9.38 per 100,000 between 2011 and 2020. While in clinical-suspected population the trend had dramatically decreased, from 1034.06 per 100,000 between 2000 and 2010 to 390.46 per 100,000 between 2011 and 2020. The reason for this phenomenon may be associated with the introduction of MS/MS into newborn screening programs in 1999 [20], the more potential patients are timely identified and treated in their newborns, the less patients develop into symptomatic patients. Since the prenatal screening for MMA has not been carried out on a large scale, the decreasing prevalence of the clinical-suspected population maybe suggests the newborn screening had played a great role in the prevention of MMA.

Interestingly, when DBS was collected at >24 h, ≥36 h, or ≥48 h after birth, the pooled prevalence estimates were all below 1 case per 100,000 newborns. While the estimate could be up to 5 cases per 100,000 when collecting after 72 h after birth, which might indicate that false-negative events probably happened when collecting DBS during 24 h–72 h after birth. Another interesting thing was that irrespective of the newborns or clinical-suspected patients, the prevalence of MMA pooled by programs adopting the combined use of MS/MS and GC/MS was higher than the prevalence pooled by programs adopting the single-use of MS/MS or GC/MS. It's hard to identify and conclude which DBS collecting time and which detection methods can obtain more reliable and sensitive results. Therefore, future diagnostic tests may be useful to determine the sensitivity and specificity of different MS methods or different DBS collection times to help policymakers and healthcare providers make more efficient screening procedures.

The treatments varied for different subtypes [7], screening program should more precisely list the subtypes of MMA. cblC might be recommended to be screened for newborns because the prevalence of cbl C was the highest among all subtypes, but long-term follow-up data and cost-benefit studies are needed to support this decision.

Several limitations of this study need to be addressed. The prevalence of MMA and its subtype may be underestimated because some studies that reported unclear MMA prevalence were excluded in this study, e.g. studies that reported “MMA/propionic acidemia” [131–135]. The lack of reporting the false positive rates, false negative rates, follow-up periods, population screening coverage, and races of the screened population in screening studies were all potential contributors leading to imprecise estimates of this study.

The prevalence estimates of MMA stratified by multiple subgroups in this review may be beneficial for further cost-effectiveness evaluation research. For example, assessing the cost-benefit of screening different subtypes of MMA, and that of screening by different technologies. Also, the results may be a reference basis for the disease control state of MMA, providing base data for a future prospective study. These results are also useful to assess the burden of MMA in a population.

Conclusions

Our review has determined the pooled prevalence and characteristics of methylmalonic acidemia in newborns and clinical-suspected populations through a systematic review and meta-analyze. Though the pooled prevalence in clinical-suspected populations has been decreased dramatically, it's still much higher than that in newborns. More efficient newborn screening strategies and closer monitoring of the clinical-suspected population for the early signs of MMA are warranted. The high prevalence of MMA in Asia and Africa should be attached importance. Further diagnostic tests were recommended for the combining-use vs single-use of MS/MS and GC/MS and for collecting blood after 72 h vs during 24–72 h after birth.
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