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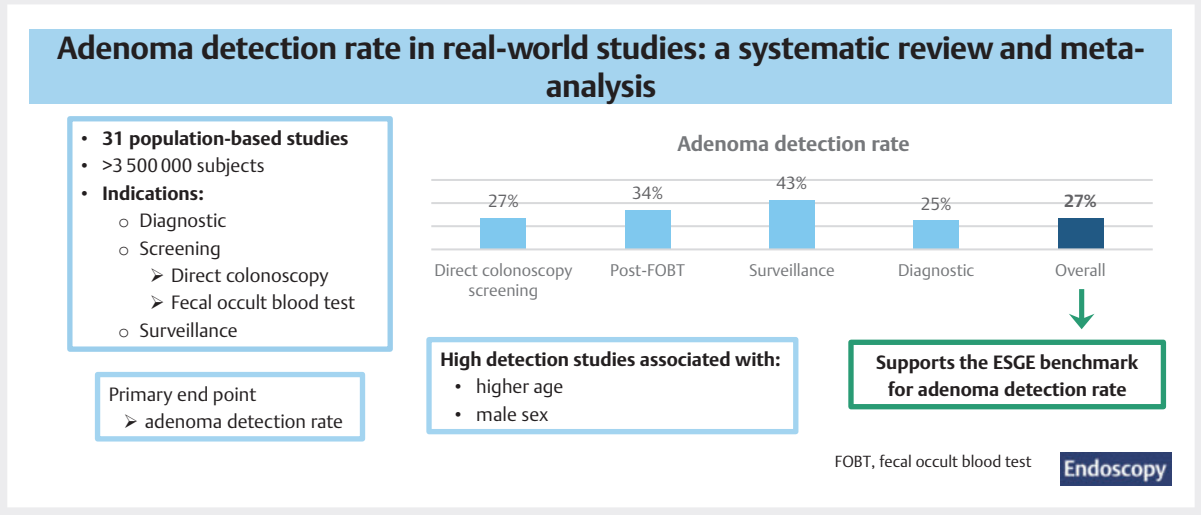
Adenoma detection rate by colonoscopy in real-world population-based studies: a systematic review and meta-analysis

GRAPHICAL ABSTRACT



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ABSTRACT

Background Adenoma detection rate (ADR) is a quality indicator set at a minimum of 25% in unselected populations by the European Society of Gastrointestinal Endoscopy (ESGE). Nevertheless, a lack of pooled observational data resembling real-world practice limits support for this threshold. We aimed to perform a systematic review with meta-analysis to evaluate the pooled rates for conventional adenoma detection, polyp detection (PDR), cecal intubation, bowel preparation, and complications in population-based studies.

Methods The PubMed, Scopus, and Web of Science databases were searched until May 2023 for populational-based studies reporting overall ADR in unselected individuals. A random-effects model was used for meta-analysis.

Results 31 studies were included, comprising 3 644 561 subjects. A high quality of procedures was noticeable, with a high cecal intubation rate and low complication rate. The overall pooled ADR, PDR, and rate of cancer detection were 26.5% (95%CI 23.3% to 29.7%), 38.3% (95%CI 32.5% to 44.1%), and 2.7% (95%CI 1.5% to 3.9%), respectively. ADR varied according to indication: screening 33.3% (95%CI 24.5% to 42.2%), surveillance 42.9% (95%CI 36.9% to 49.0%), and diagnostic 24.7% (95%CI 19.5% to 29.9%), with subgroup analysis revealing rates of 34.4% (95%CI 22.0% to 40.5%) for post-fecal occult blood test and 26.6% (95%CI 22.6% to 30.5%) for primary colonoscopy screening. Diminutive conventional adenomas yielded a pooled rate of 59.9% (95%CI 43.4% to 76.3%). The pooled rate for overall serrated lesion detection was 12.4% (95%CI 8.8% to 16.0%). Male sex and higher age were significantly associated with an ADR above the benchmark.

Conclusion This first meta-analysis relying on real-world observational studies supports the ESGE benchmark for ADR, while suggesting that different benchmarks might be used according to indication, sex, and age.

Introduction

Colorectal cancer (CRC) accounts for 10.0% and 9.4% of all new cancer cases and deaths worldwide, respectively [1]. CRC screening is available in several countries and is usually performed using either a fecal occult blood test (FOBT) or first-instance colonoscopy [2]. Following the detection of colonic polyps and CRC, a surveillance colonoscopy becomes necessary [2, 3]. Colonoscopy may also be requested for diagnostic reasons, namely to investigate symptoms and signs. In addition, there are other conditions, that may lead to a colonoscopy, such as inflammatory bowel disease (IBD) and hereditary syndromes [4, 5].

Different scientific societies have defined certain performance measures to evaluate colonoscopy quality with specific thresholds [6, 7]. The adenoma detection rate (ADR) is a well-established and widely used performance measure. American Society of Gastrointestinal Endoscopy (ASGE) guidelines have set a threshold of 25% for asymptomatic, average-risk patients [6]. The European Society of Gastrointestinal Endoscopy (ESGE) maintains the same threshold (25%), but covers a wider population – all colonoscopies in patients aged 50 years or older, excluding only colonoscopies performed in the emergency setting, with a specific therapeutic indication, or done as part of follow-up of a detected lesion or to monitor IBD. Moreover, the ADR should be monitored in all settings [7].

There is already some aggregate evidence regarding ADR, namely in asymptomatic average-risk individuals with a positive fecal immunochemical test (FIT) [8] and in control groups of randomized control trials (RCTs) [9]. Nevertheless, in a real-world setting there are not the optimized conditions presented in RCTs and it is very uncommon to perform colonoscopies solely for a specific indication. Additionally, Corley et al. [10] described that, in an unselected population, the ADR was inversely associated with the risks of interval CRC, advanced-stage interval cancer, and fatal interval cancer. Therefore, it is important to evaluate ADR in a real-world setting and, consequently, to assess the appropriateness of the benchmark proposed by the ESGE. Other performance measures were also defined by Kaminski et al. [7], namely polyp detection rate (PDR; 40%), cecal intubation rate (90%), and adequate bowel preparation rate (90%); however, to our knowledge, there is also a lack of comprehensive evidence supporting the thresholds for these in real-world population studies.

In addition, the real-world applicability of RCTs has been questioned and there is a substantial and increasing interest in leveraging real-world data for the formulation and validation of hypotheses and evidence [11, 12]. Therefore, we aimed to conduct a systematic review and random-effects meta-analysis of population-based observational studies to evaluate the overall ADR as our primary end point.

Methods

Search strategy

This study followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guidelines [13] and the Cochrane Collaboration guidelines for reporting meta-analyses [14]. The literature search was performed in three different databases: PubMed, Web of Science, and Scopus. Databases were searched from inception up to 16 May 2023, using adjusted queries (**Appendix 1s**, see online-only Supplementary material) and complemented with a backward citation strategy.

Eligibility criteria

We included observational population-based studies resembling real-world clinical practice and reporting the overall ADR. The inclusion criteria were: (i) prospective studies, patient registries, and studies based on prospectively collected databases; (ii) consecutive or randomly selected populations, including subjects submitted to colonoscopy by physicians for at least one of the three different indications: diagnostic, screening, and surveillance; and (iii) the overall "conventional" ADR was reported. No date or language restrictions were applied. Indications for colonoscopy were defined as:

- screening: direct referral for colonoscopy, colonoscopy after positive FOBT, for positive family history of colonic polyps or CRC
- surveillance: surveillance after colonic polyp or CRC diagnosis and treatment
- diagnostic: symptoms and/or signs that might be explained by colonoscopy.

The exclusion criteria were: (i) systematic or narrative reviews; (ii) guidelines, expert opinions, and editorials; (iii) animal studies [13]; (iv) RCTs; (v) less than 451 patients per analyzed population (according to the smallest sample size considered by Do et al. [15]); (vi) evaluating a specific set of individuals (e. g. post-transplant); (vii) studies excluding any of the referred indications (diagnostic, screening, and/or surveillance); (viii) retrospectively collected databases; and (ix) inclusion of serrated adenomas and/or CRC in the calculation of overall ADR.

Whenever there was more than one publication from the same database, complementary data and/or the most recent information (in case of overlapping data) were used. If complementary data were used, each study was counted individually.

Study selection and data collection

Two authors (C.F. and M.M.E.) independently screened the results and extracted the data. First, the titles and abstracts were carefully analyzed and those that did not meet the eligibility criteria were excluded. The full texts of the remaining entries were then evaluated to determine their inclusion or exclusion. Whenever a divergence occurred, it was handled by consensus, with support of the Systematic Reviews and Meta-Analyses guidelines [13] and Meta-analysis Of Observational Studies in Epidemiology checklist [16]. Different data were retrieved from the included studies (**Appendix 1s**).

Outcomes

The primary end point was the pooled detection rate of conventional adenomas. Secondary end points were the pooled rates for subgroup analysis of ADR, namely regarding study design, indications, and inception date of each cohort. Mixed-effects meta-regression was used to assess the strength of possible associations between selected covariates and the primary end point. Secondary end points also included pooled rates for: a) all types of polyps; b) advanced adenoma; c) serrated polyps; d) CRC; e) adequate bowel preparation; f) cecal intubation; e) location, morphology and size of conventional adenomas; g) adverse events and complications.

Study quality assessment

Study quality was based on the Newcastle–Ottawa Quality Assessment Scale (NOS) [17, 18] and was as described in **Appendix 1s**.

Statistical analysis

We performed a meta-analysis to calculate the pooled rates along with their corresponding 95%CIs, using a random-effects model. We assessed heterogeneity among the study outcomes to evaluate the variability in effect sizes across the included studies by using the Cochran *Q* statistical test for heterogeneity and the I^2 statistic. Sensitivity analysis (excluding one study at a time) was performed. Subgroup analyses were conducted to derive estimates within particular subsets, potentially revealing variations in effects that could explain the observed heterogeneity.

Mixed-effects meta-regression was performed to investigate how relevant characteristics might be associated with the outcome, helping to understand the factors contributing to the heterogeneity. The meta-regression model included covariates selected on the basis of scientific judgment and the absence of high multicollinearity. Multicollinearity was assessed using the Generalized Variance Inflation Factor (GVIF), with a threshold of GVIF >10 indicating high multicollinearity. The study's design (prospective, patient registry, and retrospective), most common indication (diagnostic vs. screening/surveillance), age (mean), sex (percentage of men), sample size (absolute number), and adequate bowel preparation (percentage of adequate bowel preparation) were included as fixed effects. Random effects were applied for between-study variability. ADR was considered a continuous dependent variable. The Benjamini–Hochberg procedure was performed to correct for multiple testing.

Publication bias was ascertained qualitatively by visual inspection of the funnel plot and quantitatively by Egger's test.

P values <0.05 were considered to be statistically significant. All analyses were performed using RStudio (v. 4.1.1.) and the *metafor* package.

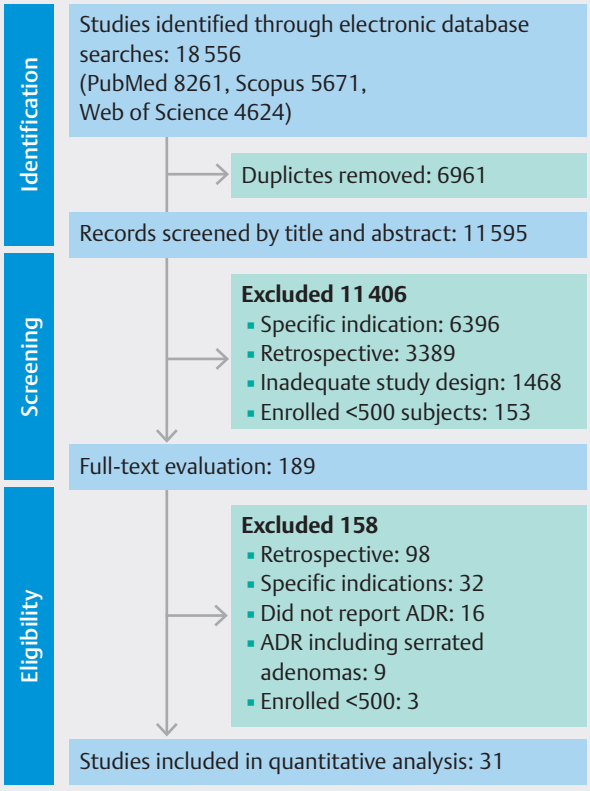
Results

Literature search and study selection

The study selection process is described in ▶ **Fig. 1**. Through this process, 31 studies (including two studies with complementary information which were considered as one) matched the eligibility criteria.

Study characteristics

The characteristics of the 31 studies included [19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49] are summarized in ▶ **Table 1**. The studies varied widely regarding their country of origin, year of publication (from 2004 to 2022, median 2013), and number of included subjects (from 477 to 2 910 174 subjects).



▶ **Fig. 1** Flow diagram of study selection and the data collection process. ADR, adenoma detection rate.

Even though we did not establish age limits, no pediatric cohorts were identified. Sixteen studies were prospective (n = 73 578 subjects; 2.0%), 10 used retrospective analysis of prospectively collected databases (n = 49 528 subjects; 1.4%) and four were patient registries (n = 3 521 455 subjects; 96.6%). Eleven studies were multicenter.

Overall, 3 644 561 subjects (48.1% male) underwent colonoscopy (no study reported a mean age <45 years). The overall distribution according to the indication was: screening 1 231 463 (33.8%), diagnostic 288 849 (7.9%), surveillance 154 735 (4.2%), other indications (including IBD and hereditary syndromes) 4955 (0.1%), or not described in 1 964 559 (53.9%). Twenty studies described the number of subjects per indication and eight described ADR per indication (**Table 1s**). Adenoma characteristics, such as location, size, and morphology were only provided in six, six, and four studies, respectively (**Table 2s**). The description of advanced adenoma varied within studies (▶ **Table 2**), with the most common definition being conventional adenomas >10 mm, and/or with high grade dysplasia (HGD), and/or a villous component. The polyp types that were included in the calculations of the reported serrated lesion detection rates also varied (**Tables 3s** and **4s**). Ten studies provided information on the rates of total complications (**Table 5s**). Nine studies reported the use of low or high definition endoscopes (▶ **Table 1**).

Study quality assessment

Overall quality was satisfactory (median 5, interquartile range [IQR] 1.75); further details in **Appendix 1s** and **Table 6s**.

▶ **Table 1** Characteristics of the studies included in the meta-analysis.

Author, year	Study period; country; setting	Indication, %	Sample size	Age mean (SD/ range), years; sex, male, %	Sedation, %; high definition scope, %	Cecal intubation rate, %; bowel prep adeq/fair, %	Withdrawal time[1], mean (SD), minutes
Prospective multicenter studies							
Afify, 2021 [19]	7/2020–12/2020; Egypt; hospital	ND	1006	45.4 (16.5); 50.8%	81.0%; 70%	95.4% adeq; 60.8%[2]	11 (6.5)
Mangas San-Juan, 2019 [20]	2/2016–12/2017; Spain; hospital and OPC	Surv 15.3% Diagn 40.3% Screen 44.4%	14 867	61.2 (9.4); 51.8%	94.0%; 74.1%	95.3%; 86.6%	8.4 (3.2)
Belderbos, 2015 [21]	11/2012–1/2013; Netherlands; hospital	Surv 20.0% Diagn 71.6% Screen 8.4%	3129	59 (15); 45.5%	90.8%; NR	94.8%; 89.7%	NR
Coriat, 2012 [22]	1/2008–1/2009; Belgium; hospital and OPC	ND	2000	Median 57.4; 49.4%	NR; NR	95.3%; 96.3%	NR
Overholt, 2011 [23]	2007 (1 month); Canada; OPC	Surv 25.4% Diagn 36.4% Screen 38.2%	15 955	59.9 (12.8); 48.2%	NR; NR	97.8%; NR	8.77 (5.86)
Prospective single center studies							
Parra-Pérez, 2020 [24]	7/2015–8/2016 ; Peru; OPC	Screen 20.5%	1378	58 (14.3); 39.6%	NR; NR	98.3%; 93.6%	NR

▶ **Table 1** (Continuation)

Author, year	Study period; country; setting	Indication, %	Sample size	Age mean (SD/ range), years; sex, male, %	Sedation, %; high definition scope, %	Cecal intubation rate, %; bowel prep adeq/fair, %	Withdrawal time[1], mean (SD), minutes
Pantone, 2016 [25]	1/2013–10/2014; Italy; hospital	ND	519	55.3 (12.8); 43.5%	100%; NR	Complete exams only; 69.4%	NR
Santos, 2015 [26]	1/2007–12/2011; Brazil; hospital	Surv 23.1% Diagn 59.0% Screen 17.9%	3623	NR; NR	NR; 100%	Complete exams only; [2]	>6 min 100%
Bouwens, 2013 [27]	2/2008–2/2012; Netherlands; hospital	Surv 9.0% Diagn 84.1% Screen 6.9%	7433	59 (16); 45.9%	NR; 100%	91.2%; 92.8%[2]	NR
Rondagh, 2012 and 2013 [28, 29]	2/2008–2/2009; Netherlands; hospital	Surv 12.4% Diagn 80.5% Screen 7.1%	2310	58.4 (16.2); 46.1%	NR; 100%	91.2%; NR	NR
Forsberg, 2012 [30]	6/2002–10/2006; Sweden; hospital	ND	745	51.1; 43%	NR; NR	94.2%; NR	NR
Gromski, 2011 [31]	3/2010–2/2011; Korea; hospital	Screen 53.5%	1262	54.2 (13); 48.5%	100%; 0%	100%; NR	10.2 (3.4)
Morini, 2009 [32]	1/2016–12/2016; Italy; hospital	Surv 26.0% Diagn 58.0% Screen 16.0%	1082	61 (38–92); 65.0%	100%; NR	94.1%; 96.4%2	Median 6.4 min (IQR 6–8)
Chan, 2009 [33]	9/2006–9/2007; USA; hospital	Surv 43.8% Diagn 22.0% Screen 37.7%	477	63.7 (13); 96.9%	100%; NR	90.4%; 64.8%	>6 min 96.8%
Park, 2006 [34]	7/2003–3/2004; Korea; hospital	Surv 11.5% Diagn 43.2% Screen 27.6% Others 17.7%	17 307	52.3; 57.1%	100%; NR	99.1%; NR	NR
Denis, 2006 [35]	6/2002–10/2002; France; hospital	Surv 20.2% Diagn 42.1% Screen 21.9%	500	63 (15–92); 50.8%	98%; NR	92%; 92%	NR
Patient registries							
Sonnenberg, 2022 [36]	12/2008–3/2020; USA; OPC	Screen 33.6%	2 910 174	59.8 (13.8); 48.8%	NR; NR	NR; NR	NR
Anderson, 2014 [37]	4/2009–3/2011; USA; hospital and OPC	Surv 25.2% Diagn 20.8% Screen 53.5%	13 022	59 (9); 47.0%	NR; NR	Complete exams only; 98.5%	<6 min 21%, >6 min 79%
Hernandez, 2014 [38]	1/2007–9/2012; USA; OPC	Surv 27% Diagn 31% Screen 42%	368 157	NR; 44.4%	NR; NR	96.0%; 84.9%	<6 min 4.3%, >6 min 95.7%
Mansmann, 2008 [39]	1/2006–12/2006; Germany; OPC	Surv 15.8% Diagn 54.6% Screen 29.6%	230 102	NR; 43.2%	92.9%; NR	97.4%; 98.5%	NR
Retrospective multicenter studies							
Watson, 2022 [40]	7/2020–7/2021; Australia; hospital	ND	3497	60.8 (13.8); 52.6%	NR; NR	96.1%; 94.0%	9.18
Retrospective single center studies							
Cavicchi, 2019 [41]	1/2016–12/2017; France; OPC	Surv 26.0% Diagn 37.2% Screen 28.8% Others 8.0%	11 682	Median 58; 45.7%	NR; 100%	99.3%; 94.8%	8.80

▶ **Table 1** (Continuation)

Author, year	Study period; country; setting	Indication, %	Sample size	Age mean (SD/ range), years; sex, male, %	Sedation, %; high definition scope, %	Cecal intubation rate, %; bowel prep adeq/fair, %	Withdrawal time[1], mean (SD), minutes
Nalankili, 2019 [42]	8/2011–8/2015; Australia; OPC	Surv 38.0% Diagn 44.5% Screen 12.1% Therap 5.4%	841	58.9 (14.2); 54.0%	100%; 100%	97.5%; 91.1%	NR
Al-Najami, 2017 [43]	9/2013–6/2015; Denmark; hospital	Surv 44.3% Diagn 25.1% Screen 25.1% Others 5.9%	999	Median 65.1 (12); 54.7%	NR; NR	Complete exams only; NR	NR
Ochipinti, 2015 [44]	1/2011–12/2011; Italy; hospital	Surv/Screen 26% Diagn 74%	2974	64.1 (11); 55.2%	NR; NR	98.5%; 77.0%	NR
Khumbari, 2013 [45]	6/2010–7/2011; Australia; OPC	Surv 19.2% Diagn 56.0% Screen 23.3% Others 1.5%	1000	57.6 (13.6); 50.1%	NR; 100%	99.7%; 99.5%2	NR
Plummer, 2012 [46]	3/2007–4/2011; Jamaica; OPC	Surv 10.0% Diagn 69.0% Screen 16.8% Others 11.4%	1250	60.6; 43.5%	NR; NR	96.0%; NR	NR
Bhangu, 2012 [47]	6/2007–1/2010; UK; hospital	Surv 22.6% Diagn 55.8% Screen 14.6% IBD 7.0%	10026	Median 64; 50.2%	NR; NR	90.2%; NR	NR
Millan, 2008 [48]	1/1998–12/2004; USA; OPC	ND	16335	NR; NR	NR; NR	96.5%; NR	NR
Arora, 2004 [49]	NR; UK; hospital	ND	924	NR; 43.5%	NR; NR	95.0%; NR	NR

adeq, adequate; Diagn, diagnostic; IBD, inflammatory bowel disease; IQR, interquartile range; Med, median; ND, not described; NR, not reported; OPC, outpatient clinic; Screen, screening; Surv, surveillance; Therap, Therapeutic.
[1] Without therapy being performed.
[2] Excluded poor.

Adenoma detection rate

The pooled ADR (primary end point) was 26.5% (95%CI 23.3% to 29.7%; I^2 = 99.9%, *Q* test statistically significant) (▶ **Fig. 2**).

When studies describing ADR per indication were evaluated, the pooled ADR was 33.3% (95%CI 24.5% to 42.2%; I^2 = 99.7%; n = 7) for screening, 42.9% (95%CI 36.9% to 49.0%; I^2 = 98.2%; n = 7) for surveillance, and 24.7% (95%CI 19.5% to 29.9%; I^2 = 99.5%; n = 5) for diagnostic purposes (▶ **Fig. 3**; **Table 7s**). Individuals who underwent screening colonoscopy after a positive FOBT had a pooled ADR of 34.4% (95%CI 22.0% to 40.5%; I^2 = 99.5%; n = 5); individuals referred for direct colonoscopy screening had a pooled ADR of 26.6% (95%CI 22.6% to 30.5%; I^2 = 97.0%; n = 4) (**Table 7s**).

The linear regression model suggested that increasing the percentage of subjects undergoing colonoscopy for surveillance was associated with an increase in ADR (b = 0.36; P = 0.04). Although the linear regression model evaluating the relationship between the percentage of subjects assessed for diagnostic purposes in each cohort and overall ADR did not reach statistical significance, the observed trend (regression line) suggests that an increase in the number of subjects undergoing colonoscopy for diagnostic purposes leads to a decrease in overall ADR (**Fig. 1s**). The pooled rate for studies including a majority of subjects assessed for diagnostic purposes was 27.1% (95%CI 21.7% to 31.1%; I^2 = 99.5%; n = 12) and for screening/surveillance was 31.2% (95%CI 25.9% to 36.5%; I^2 = 99.8%; n = 9).

The pooled rates for ADR in prospective, patient registry, and prospectively collected studies were 27.0% (95%CI 22.8% to 31.3%; I^2 = 99.3%; n = 16), 28.9% (95%CI 20.3% to 37.4%; I^2 = 99.9%; n = 4), and 24.7% (95%CI 18.7% to 30.7%; I^2 = 99.6%; n = 10), respectively (**Table 7s**). Given that patient registries included more than 90% of the subjects, a subgroup analysis without these studies was also performed, but revealed no significant difference in the outcome: 26.1% (95%CI 22.7% to 29.6%; I^2 = 99.5%; n = 26).

Subgroup analysis according to study design and indication achieved only a slight improvement of the I^2 (**Table 7s**). The linear regression model evaluating the relationship between co-

▶ **Table 2** Summary of the rates of polyp detection, adenoma detection (globally, per colonoscopy, and per positive colonoscopy) and rates of colorectal cancer (CRC).

Author, year	Polyp detection rate, %	Adenoma detection rate, %	Adenomas per colonoscopy, rate	Adenomas per positive colonoscopy, rate	Advanced adenoma rate, %	Serrated lesion detection rate, %	CCR detection rate, %
Prospective multicenter							
Afify, 2021 [19]	32.7%	15%	NR	NR	2.5%[1]	NR	2.5%
Mangas San-Juan, 2019 [20]	54.9%	38.0%	0.93	2.46	16.6%[2]	12.5%[3]	3.9%
Belderbos, 2015 [21]	45.2%	31.8%	0.60	1.89	NR	NR	NR
Coriat, 2012 [22]	NR	19.2%	NR	NR	4.5%[2]	NR	2.0%
Overholt, 2011 [23]	42.7%	24.9%	NR	NR	NR	NR	0.7%
Prospective single center							
Parra-Pérez, 2020 [24]	NR	24.4%	0.40	1.65	NR	8.7%[3]	NR
Pantone, 2016 [25]	35%	21%	0.26	1.23	NR	NR	3%
Santos, 2015 [26]	46.2%	31.3%	0.57	1.82	NR	NR	NR
Bouwens, 2013 [27]	NR	28.5%	0.56	1.98	NR	14.0%[4]	NR
Rondagh, 2012 and 2013 [28, 29]	93%	26.8%	0.50	1.89	13.9%[5]	NR	NR
Forsberg, 2012 [30]	27.5%	10.0%	0.15	1.53	2.8%[2]	NR	0%
Gromski, 2011 [31]	33.2%	22.3%	NR	NR	4.4%	33.2%	22.3%
Morini, 2009 [32]	40%	34%	0.37	1.08	NR	NR	2%
Chan, 2009 [33]	70.9%	46.1%	NR	NR	18.0%	70.9%	46.1%
Park, 2006 [34]	24.2%	30.7%	0.39	1.23	6.8%[2]	NR	0.3%
Denis, 2006 [35]	37.0%	28.0%	87.6%	NR	10.3%	NR	5.3%
Patient registries							
Sonnenberg, 2022 [36]	NR	41.2%	NR	NR	NR	NR	1.0%
Anderson, 2014 [37]	NR	26.3%	NR	NR	NR	8.8%[6]	NR
Hernandez, 2014 [38]	NR	27.5%[7]	NR	NR	NR	NR	NR
Mansmann, 2008 [39]	NR	20.4%	NR	NR	NR	NR	1.5%
Retrospective multicenter							
Watson, 2022 [40]	36.5%	25.6%	NR	NR	NR	5.4%[6]	2%
Retrospective single center							
Cavicchi, 2019 [41]	36.1%	29.2%	0.50	1.71	8.9%[8]	8%[6]	NR
Nalankili, 2019 [42]	NR	41.1%	NR	NR	NR	18.9%[6]	1.0%

▶ **Table 2** (Continuation)

Author, year	Polyp detection rate, %	Adenoma detection rate, %	Adenomas per colonoscopy, rate	Adenomas per positive colonoscopy, rate	Advanced adenoma rate, %	Serrated lesion detection rate, %	CCR detection rate, %
Al-Najami, 2017 [43]	NR	26.3%	0.59	2.04	NR	NR	0.7%
Ochipinti, 2015 [44]	41.3%	29.3%	0.65	2.21	NR	22.4%[4]	NR[9]
Khumbari, 2013 [45]	NR	34.6%	NR	NR	9.0%[2]	NR	1.3%
Plummer, 2012 [46]	NR	11%	NR	NR	NR	NR	10%
Bhangu, 2012 [47]	33.5%	19.2%	NR	NR	NR	NR	NR
Millan, 2008 [48]	NR	21.0%	NR	NR	NR	NR	NR
Arora, 2004 [49]	15.1%	10.3%	NR	NR	NR	NR	8.9%

ND, not described; NR, not reported.
[1] High grade dysplasia.
[2] High grade dysplasia, or villous, or 10 mm.
[3] Proximal hyperplastic polyp, >5 hyperplastic polyps, sessile serrated adenoma, and traditional serrated adenoma.
[4] All serrated polyps.
[5] >10 mm, high grade dysplasia, >3, cancer.
[6] Excluded hyperplastic polyp rectum and sigmoid.
[7] From graph.
[8] >10 mm, high grade dysplasia, villous, cancer.
[9] Only absolute.

hort date and overall ADR did not reach statistical significance ($P = 0.73$). Regarding the subgroup of studies with cohorts before and after 2014 [10], no significant difference was identified between the ADRs (26.2%, 95%CI 22.5% to 29.8%; $I^2 =$ 99.9% and 27.7%, 95%CI 21.3% to 34.2%; $I^2 = 99.3\%$, respectively).

Sensitivity analysis and meta-regression:

Sensitivity analysis revealed that there was no single study that significantly affected the pooled estimates for ADR (**Table 8s**). The meta-regression model included ten distinct studies. Cohorts including a majority of subjects assessed for diagnostic purposes ($b = -0.10$, 95%CI −0.16 to −0.03) and from patient registries ($b = -0.12$, 95%CI −0.18 to −0.07) were significantly related to ADR. The GVIF was less than 10 for all included variables (**Table 9s**, **Fig. 2s**). Evaluation of our model's robustness revealed no significant residual heterogeneity (test for residual heterogeneity, $P = 0.32$; test for moderators, $P<0.001$). According to the visual inspection of the funnel plot (**Fig. 3s**) and to the results of Egger's test ($z = -0.19$; $P = 0.85$), no strong statistical evidence of publication bias or small-study effects was assumed.

Low versus high detection rate studies

We also performed subgroup analysis of the studies with overall ADRs above and below the ESGE benchmark (25%). There were 12 studies (40.0%) that reported ADRs <25% (low detection rate studies) and the remaining 18 (60.0%) reported ADRs >25% (high detection rate studies). The percentage of male subjects was significantly lower in low detection studies (median 43.5% [IQR 5.6%] vs. 50.8% [IQR 8.6%]; $P = 0.007$). Age was significantly higher in the high detection studies (median 55.3 years [IQR 3.8%] vs. 59 years [IQR 2.05]; $P = 0.03$).

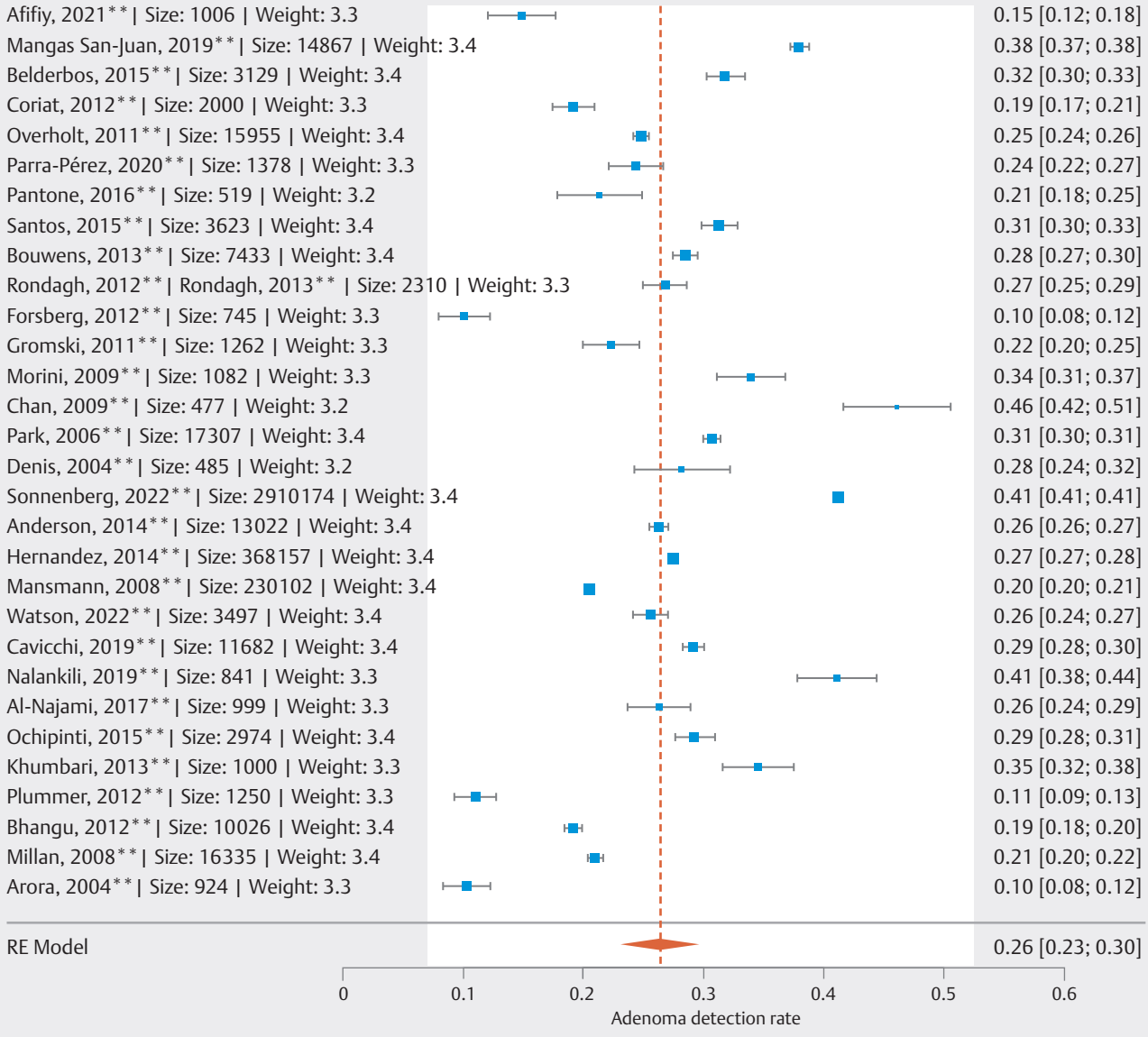
The advanced ADR was significantly lower in low detection studies (3.6% [IQR 12.5%] vs. 10.3% [IQR 6.3%]; $P = 0.01$) (**Table 10s**). The indications were less reported in the subgroup with lower ADRs (50.0% vs. 94.4%).

Location, morphology, and size of conventional adenomas

Meta-analysis of the proportion of polyps measuring <5 mm yielded a pooled rate of 59.9% (95%CI 43.4% to 76.3%; $I^2 =$ 99.3%; n = 5). The estimated overall proportion of proximal adenomas was 48.2% (95%CI 39.0% to 57.3%; $I^2 = 98.7\%$; n = 6) and of nonpedunculated polyps was 18.9% (95%CI 0.6% to 37.3%; I^2 = 99.8%; n = 4) (**Table 7s**)

Advanced adenoma, polyp, and CRC rate

The overall pooled rate for advanced adenomas was 8.8% (95% CI 5.7% to 12.0%; $I^2 = 99.3$; n = 11). When this was restricted to the most common description (HGD, and/or villous, and/or ≥10 mm), the pooled rate was 8.0% (95%CI 3.3% to 12.7%; $I^2 =$ 99.5; n = 5). The PDR was 38.3% (95%CI 32.5% to 44.1%; $I^2 =$ 99.7%; n = 17) and the CRC detection rate was 2.7% (95%CI 1.5% to 3.9%; $I^2 = 99.9\%$; n = 18) (**Table 7s**).



▶ **Fig. 2** Forest plot of adenoma detection rate in the included population-based studies (weights described as percentage of total).

Serrated lesion detection rate

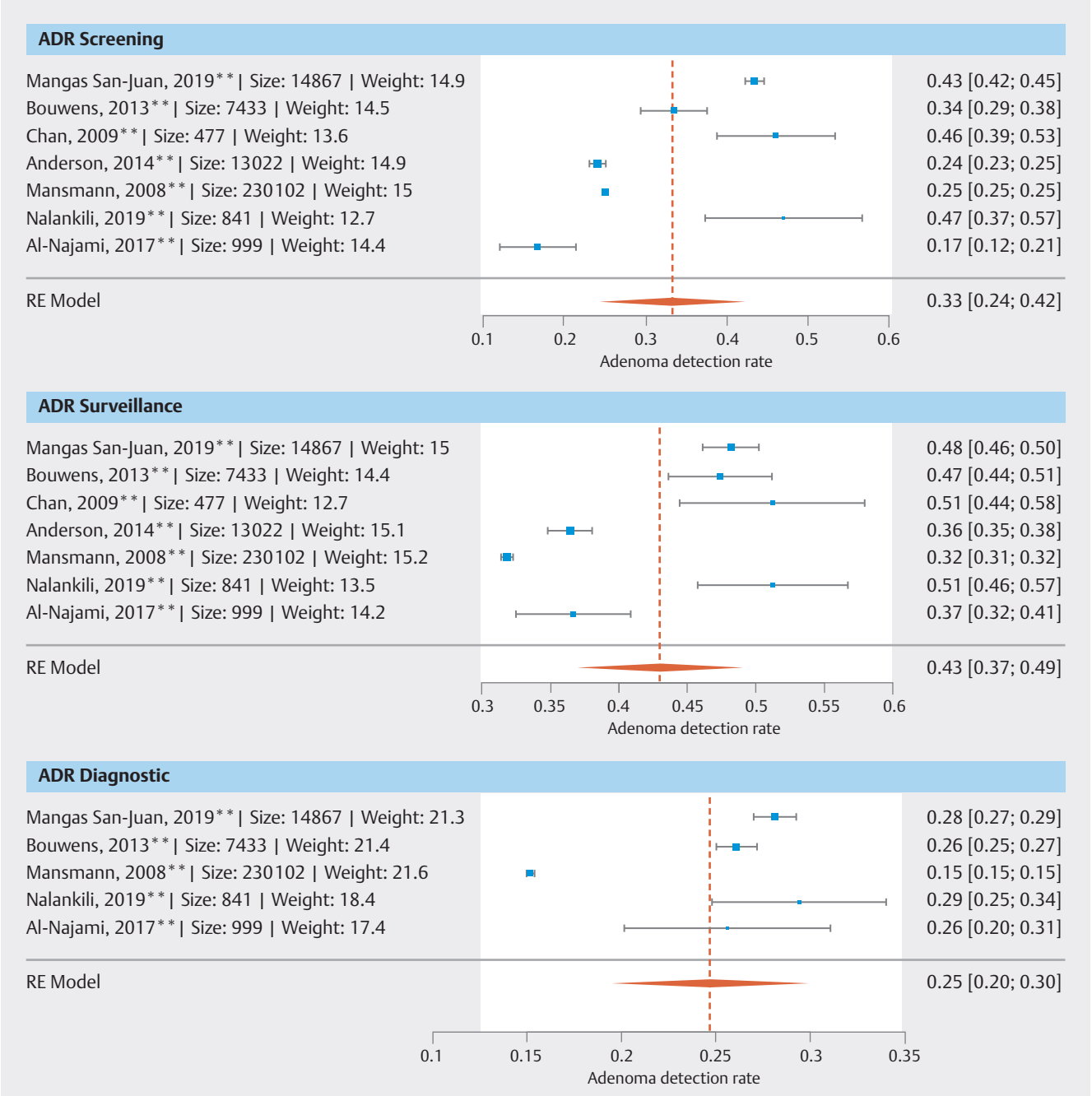
The overall pooled rate of serrated lesion detection was 12.4% (95%CI 8.8% to 16.0%; I^2 = 99.5; n = 9). The pooled rate of detection of proximal serrated lesions (one sessile serrated adenoma/polyp [SSA/P], traditional serrated adenoma [TSA], or hyperplastic polyp [HPP] of any size proximal to the sigmoid was the most common description) was 10.2% (95%CI 4.5% to 16.0%; I^2 = 99.6%; n = 4) (**Table 7s**). The pooled detection rates for SSA/Ps and/or TSAs, and HPPs were 4.5% (95%CI 0.36 to 8.6%; I^2 = 99.9%; n = 6) and 19.2% (95%CI 13.5% to 24.8%; I^2 = 99.5%; n = 4), respectively.

Cecal intubation and bowel preparation

The cecal intubation rate was 95.7% (95%CI 94.6% to 96.9%; I^2 = 99.8%; n = 25) and bowel preparation was deemed adequate in 89.7% of procedures (95%CI 85.3% to 94.2%; I^2 = 99.9%; n = 18) (**Table 7s**)

Withdrawal time

The weighted mean withdrawal time was 9.0 minutes (n = 6), with no study reporting a value of <6 minutes (▶ **Table 1**). When reported according to the 6-minute threshold, only 5% of colonoscopies (10 822/206 353) were less than the threshold (n = 4).



▶ **Fig. 3** Forest plot of adenoma detection rate (ADR) in the included population-based studies (weights described as percentage of total) according to the indication: **a** screening; **b** surveillance; **c** diagnostic.

Adverse events

The pooled rates for reported complications and perforations were also calculated. An overall complication rate of 0.4% (95% CI 0.1% to 0.6%; $I^2 = 98.7\%$; n = 9) and pooled perforation rate of 0.04% (95%CI 0.01% to 0.08%; $I^2 = 84.0\%$; n = 9) were achieved (**Table 7s**).

Discussion

In our systematic review and meta-analysis of real-world studies, including more than 3 million subjects, we found that the pooled ADR was 26.5% (95%CI 23.3% to 29.7%; $I^2 = 99.9\%$, *Q* test statistically significant), being very similar to the ESGE benchmark. While the overall quality assessment was satisfactory, we observed considerable variability in the reported information: sex, cecal intubation, and bowel preparation were frequently described, while other pertinent measures such as

withdrawal time and the use of high definition scopes were often missing. Moreover, a large degree of variability was observed between the studies in some of the definitions, namely in the descriptions of screening population, advanced adenoma, and serrated polyps. Efforts should be made to standardize definitions to generate meaningful and widely agreed real-world evidence.

Recently, Hassan et al. [9] reported a pooled ADR in the control arms of RCTs (including screening, surveillance, and diagnostic indications) of 37.5% (95%CI 34.6% to 40.5%; I^2 = 95.1%). Although this result is significantly higher, it comes from the optimized conditions within RCTs and, where the indication was described, no colonoscopies were performed for diagnostic purposes.

The ADR was higher in surveillance colonoscopies, followed by screening, and lower in those performed for diagnostic purposes. This was further illustrated by a positive association between the number of subjects undergoing colonoscopy for surveillance and the ADR. These data highlight the impact of different populations on ADR, reinforce the need to have a balanced population when using the ESGE benchmark, and demonstrate the relevance of applying specific thresholds for particular populations. In true screening populations, the ADR tends to be at an intermediate level between the levels for surveillance and diagnostic examinations; consequently, overall ADRs for the three groups of patients combined tend to be closer to the ADR screening benchmark [50]. This is supported by our analysis as the overall ADR and the ADR for primary screening colonoscopy presented similar values (26.5% [95%CI 23.3% to 29.7%] vs. 26.6% [95%CI 22.6% to 30.5%]). If, for any reason, there is a significant imbalance in this distribution, the ADR might be lower than the benchmark, while performance should still be deemed adequate. This may occur for example in an unbalanced population with a predominance of subjects undergoing colonoscopy for diagnostic purposes.

There is evidence that the thresholds for post-FOBT colonoscopies should be higher than those applied for primary screening colonoscopies [51,52]. In our study, a lower ADR was achieved in subjects who underwent primary colonoscopy screening compared with subjects undergoing colonoscopy after a positive FOBT (26.6% [95%CI 22.6% to 30.5%] vs. 34.4% [95%CI 22.0% to 40.5%], respectively). These findings should raise awareness regarding the need to clearly define, describe, and standardize screening populations within studies to achieve consistent results. Mohan et al. [8] reported a pooled ADR in FIT-positive subjects of 47.8% (95%CI 44.1% to 51.6%). This higher result may be explained because, while the study encompasses several population-based studies, it also included RCTs. Moreover, the inclusion criteria required only average-risk asymptomatic individuals undergoing colonoscopy after a positive screening FIT test, which does not resemble the most common scenario in clinical practice. Zorzi et al. [53] also demonstrated that the ADR in FIT-positive subjects is partly determined by the cutoff value. In our study, cutoffs were described in only two of the included studies [20,43] and consequently this might impact our achieved ADR.

Although there is relevant evidence supporting a good correlation between ADR and PDR (and consequently its use as a surrogate marker) [54], in our study, PDR did not achieve the target value of 40% proposed by the ESGE. In turn, this may reinforce the preferential use of histology as a definitive result in observational studies.

Advanced adenomas were described differently across the studies. Nevertheless, we achieved a pooled rate for the most commonly accepted definition (HGD, and/or villous, and/or ≥10 mm) of 8.8%. This is the first reported pooled rate for advanced adenomas in population-based studies and should be further explored.

The pooled rate for cecal intubation was 95.7% (above the 95% target standard). Conversely, the pooled rate for adequate bowel preparation was slightly below the minimum threshold (90%). This may have been due to an inaccurate description of bowel preparation within the studies, as a qualitative description was given in most of the studies. Therefore, it is advisable to encourage the use of bowel preparation scores to enable a more quantitative and standard analysis of this quality measure.

In our study, we achieved an overall pooled detection rate for serrated lesions of 12.4% and a proximal serrated lesion detection rate of 10.2%. The latter is concordant with the benchmark proposed by Anderson et al. [55] in a screening population. This reinforces the possibility of using the proximal serrated lesion detection rate and its respective benchmark in clinical practice.

Notwithstanding, this study has some limitations. Although we included more than 3 million subjects, 80% were from one single study [36]. A random-effects meta-analysis was performed to account for both within-study and between-study variance and sensitivity analysis revealed that there was no single study that significantly impacted the ADR. Despite the extensive literature search, we included only 31 papers. This is explained by the rarity of reporting ADR for unselected populations and because we decided to exclude studies based on retrospectively identified data. Although we aimed to assess the ESGE benchmark, we did not exclude cohorts with subjects under 50 years of age or cohorts with subjects who underwent colonoscopy for other indications. Nevertheless, there were no pediatric cohorts and the mean age was above 45 years in all studies (>50 years in 96.7%; n = 30), while the number of subjects who underwent colonoscopy for other indications was relatively low (n = 4955; 0.14%) (▶ **Table 1**).

Owing to the inclusion of observational studies that resemble real-world practice, we expected high heterogeneity (as previously found in other related meta-analyses [8,18]). Our results confirmed significant heterogeneity as measured by the calculated I^2. Sensitivity analysis and subgroup analysis had a slight impact on the outcome and I^2. On the other hand, the meta-regression model identified diagnostic indications and patient registry data as being significantly related to ADR, helping to better understand the heterogeneity. It is however important to acknowledge that our meta-regression model incorporated only 10 studies, which may impact its conclusions and applicability. The Cochrane handbook suggests overfitting

should be considered, especially when fewer than 10 studies are included [14]. Finally, although several variables were collected for our analysis, some variables that are potentially impactful on ADR, such as obesity and smoking status, were not described or available in all studies, which may have contributed to the heterogeneity that was not explained by our meta-regression and subgroup analysis.

In conclusion, this is the first aggregate analysis evaluating ADR and other performance measures in a real-world setting, providing objective evidence to support the ESGE benchmark. Moreover, we were able to identify variables that significantly impacted the ADR rate and highlight the need to set different benchmarks according to varying indications for colonoscopy, age, and sex. While introducing novel insights through the examination of observational data, this meta-analysis also underscores the expectation of accumulating additional accurate real-world data, emphasizing the ongoing pursuit of evidence-based findings.

Conflict of Interest

The authors declare that they have no conflict of interest.

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