

Differential diagnosis of pancreatic cancer by single-shot echo-planar imaging diffusion-weighted imaging

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(DWI) to differentiate between malignant and benign pancreatic lesions.

METHODS: A computerized search was performed on PubMed, MEDLINE and EMBASE up to August 2014. Nine studies (10 sets of data) with a total of 304 malignant pancreatic lesions and 188 benign pancreatic lesions were included. The characteristics of each study included the study name, year of publication, magnetic resonance modalities used, patient population, strength of field, pulse time, repetition time, echo time (TE), maximum b factor, mean age, mean body weight, fat suppression, number of benign and malignant lesions, and true positive, true negative, false positive and false negative results. All analyses were performed using Meta-DiSc and Stata 11.0.

RESULTS: The pooled sensitivity and specificity of single-shot EPI DWI were 0.83 (95%CI: 0.79-0.87) and 0.77 (95%CI: 0.70-0.83), respectively. The positive likelihood ratio and negative likelihood ratio were 5.09 (95%CI: 2.19-11.84) and 0.23 (95%CI: 0.15-0.36), respectively. The *P* value for the χ^2 heterogeneity for all pooled estimates was < 0.05 . From the fitted summary receiver operating characteristic curve, the area under the curve and Q* index were 0.89 and 0.82, respectively. Publication bias was not present ($t = 0.58$, $P = 0.58$). Meta-regression analysis indicated that fat suppression, mean age, TE, and maximum b factor were not sources of heterogeneity (all $P > 0.05$).

CONCLUSION: Single-shot EPI DWI is useful to differentiate between malignant and benign pancreatic lesions. Lesion size ≥ 2 cm is the limit for the diagnosis of early lesions.

Key words: Meta-analysis; Single-shot echo-planar imaging; Diffusion-weighted imaging; Pancreatic cancer; Differential diagnosis

Abstract

AIM: To investigate the diagnostic ability of single-shot echo-planar imaging (EPI) diffusion-weighted imaging

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Core tip: We performed a meta-analysis to investigate the diagnostic capability of single-shot echo-planar imaging (EPI) diffusion-weighted imaging (DWI) to differentiate between malignant and benign pancreatic lesions. Single-shot EPI DWI was useful to differentiate between malignant and benign pancreatic lesions. Lesion size ≥ 2 cm was the limit for the diagnosis of early lesions.

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INTRODUCTION

Pancreatic ductal adenocarcinoma accounts for 85%-90% of all solid pancreatic tumors and is the fourth leading cause of cancer-related death^[1]. In 2014, it is estimated that there will be 46420 new cases of pancreatic cancer and an estimated 39590 people will die from this disease (<http://seer.cancer.gov/>). The only chance for a cure in pancreatic adenocarcinoma is surgery. Most of the time, by the time the tumor presents, it is already invasive. The 5-year survival rate of patients with pancreatic adenocarcinoma is dismal, being $< 10\%$. At initial diagnosis, fewer than 10% of patients can undergo surgical resection, which is the only potential curative treatment^[2]. Hence, early detection and characterization, followed by appropriate treatment, are currently the most effective strategies to reduce pancreatic cancer mortality^[1,3-5].

Diffusion-weighted (DW) imaging is a magnetic resonance imaging technique that provides unique information related to the diffusion of water molecules in the tissue, and allows estimation of cellularity and tissue structure^[6]. Recent reports have shown that the apparent diffusion coefficient (ADC) can be used to detect and characterize malignant and benign pancreatic lesions. Pancreatic cancer tissue has a significantly lower ADC value than that of normal pancreatic tissue, mass-forming focal pancreatitis, and autoimmune pancreatitis^[7,8]. DWI of the upper abdomen is a technical challenge because of artifacts secondary to heart and bowel motion, and field inhomogeneity related to parenchyma-gas interfaces.

With EPI, the information in the k-space can be acquired in a single shot. The advantage of using single-shot EPI as a readout sequence is that only one excitation is necessary, and hence the DW images become less sensitive to subject motion^[9]. The implementation of ultrafast imaging of single-shot EPI has made DWI of the upper abdomen a feasible option, and is useful to differentiate malignant from benign liver lesions^[10-13]. The diagnostic ability of

single-shot EPI DWI for the pancreas has not yet been defined. In the present study, we performed a meta-analysis to evaluate the diagnostic ability of single-shot EPI DWI to differentiate between malignant and benign pancreatic lesions.

MATERIALS AND METHODS

Search strategy

We performed a search of PubMed, MEDLINE and EMBASE up to August 2014. The following search terms were used: "pancreatic and diffusion-weighted imaging", "pancreatic and diffusion weighted imaging", "pancreatic and diffusion", "pancreas and diffusion-weighted imaging", "pancreas and diffusion weighted imaging", and "pancreas and diffusion". The search was limited to English language studies only.

Eligibility criteria for study selection

Studies were included in this analysis if: (1) single-shot EPI DWI data were obtained using either a 1.5 or 3.0 T MR scanner; (2) applied field strength was 1.5 or 3 T to represent common technical standards used for clinical pancreatic imaging; (3) the diagnostic criteria of the malignant or benign pancreatic lesions were clearly stated; and (4) data were available to fill out cross-tabs to assess true-positive (TP), true-negative (TN), false-positive (FP) and false-negative (FN) cases.

Data collection

The characteristics of each study, including study name, year of publication, MR modalities used, patient population, strength of field, pulse time, repetition time (TR), echo time (TE), maximum b factor, mean age, mean body weight, fat suppression, number of benign and malignant lesions, and TP, TN, FP and FN results, are shown in Tables 1 and 2.

Statistical analysis

The statistical methods of this study were reviewed by xiaoyuan from the Second Affiliated Hospital of Fujian Medical University. All analyses were performed using Meta-DiSc and Stata 11.0 (StataCorp, College Station, TX, United States). The DerSimonian-Laird random-effects model was used to pool together the final sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR). Publication bias was evaluated. We also performed a meta-regression analysis by adding covariates to the summary receiver operating characteristic (SROC) curve using the Moses-Shapiro-Littenberg method^[14,15]. For all tests, $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Study selection and data extraction

The initial database search of PubMed and EMBASE identified 170 relevant articles that were published up

Table 1 Diffusion-weighted imaging studies of pancreatic lesions

No.	Ref.	Year of publication	Patient population	MRI unit	Field (T)	TR (ms)	TE (ms)	Max b factor (s/mm ²)	Mean age (yr)	FS	Mean size (cm)
1	Muhi <i>et al</i> ^[21]	2011	Japanese	GE	1.5	8000-10000	73	1000	66.1	Yes	2.6
2	Lemke <i>et al</i> ^[20]	2009	Germany	Siemens	1.5	1300	60	800	65.1	Yes	2.8
3	Sandrasegaran <i>et al</i> ^[22]	2011	American	Siemens	1.5	1500	71	800	68.0	Yes	2.0
4	Sandrasegaran <i>et al</i> ^[23]	2013	American	Siemens	1.5	1500	71	800	66.2	Yes	3.6
5	Kartalis <i>et al</i> ^[17]	2009	Sweden	Siemens	1.5	4600	77	500	NA	Yes	NA
6	Lee <i>et al</i> ^[19]	2008	Korean	Siemens	1.5	2100	72	1000	57.4	NA	3.6
7	Ichikawa <i>et al</i> ^[2]	2007	Japanese	GE	1.5	8000-10000	73	1000	62.0	Yes	2.8
8	Huang <i>et al</i> ^[16]	2011	Chinese	GE	3.0	5700	55	1000	58.9	Yes	3.4
9	Klauss <i>et al</i> ^[21]	2011	Germany	Siemens	1.5	1300	60	800	62.8	Yes	3.5

TR: Repetition time; TE: Echo time.

Table 2 Diffusion-weighted imaging studies of pancreatic lesions

No.	Ref.	Benign lesions	Malignant lesions	TP	FP	FN	TN
1	Muhi <i>et al</i> ^[21]	10	54	52	0	2	10
2	Lemke <i>et al</i> ^[20]	14	23	17	2	6	12
3	Sandrasegaran <i>et al</i> ^[22]	45	25	20	26	5	19
4	Sandrasegaran <i>et al</i> ^[23]	23	13	9	4	4	19
5	Kartalis <i>et al</i> ^[17]	24	12	11	2	1	22
6a	Lee <i>et al</i> ^[19]	13	47	34	3	13	10
6b	Lee <i>et al</i> ^[19]	13	47	41	4	6	9
7	Ichikawa <i>et al</i> ^[2]	23	26	25	0.3	1	22.7
8	Huang <i>et al</i> ^[16]	14	37	31.7	1.9	5.3	12.1
9	Klauss <i>et al</i> ^[18]	9	20	13	0	7	9

TP: True-positive; TN: True-negative; FP: False-positive; FN: False-negative cases.

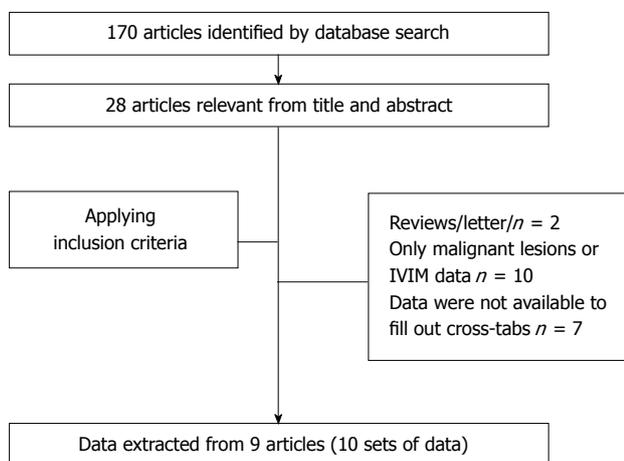


Figure 1 Selection process of the articles. Pooled analysis.

to August 2014. The initial screening by one reviewer reduced this to 28 articles. After applying the inclusion criteria, nine articles^[2,16-23] were selected for data extraction (10 sets of data) (Figure 1).

Description of studies

The meta-analysis included 304 malignant and 188 benign pancreatic lesions from nine studies (10 sets of data) (Table 1).

Eight studies used a 1.5 T MRI scanner (Nos. 1-7 and 9) and the other (No. 8) used a 3 T scanner. Seven

studies (Nos. 2-6, 8 and 9) used a DWI sequence with TR in the range of 1300-5700 ms, and two studies (Nos. 1 and 7) used a DWI sequence with TR of 8000-10000 ms. Typical acquisition parameters included TE of ≥ 55 ms (Nos. 1-9 range: 55-73 ms). Typical acquisition parameters included maximum b factor of 800 or 1000 ms (No. 1-4 and No. 6-9). One study (No. 6) did not provide information on the fat suppression technique used. One study (No. 5) did not provide information on the mean size of malignant tumors. The mean age of patients with malignant pancreatic lesions was 63.3 years (No. 1-4 and No. 6-9). The results of all analyses are reported in Tables 1 and 2.

Synthesis of general diagnostic parameters

Figure 2 shows the forest plots of sensitivity (Figure 2A), specificity (Figure 2B), PLR (Figure 2C) and NLR (Figure 2D), of DWI for differential diagnoses between malignant and benign pancreatic lesions.

The pooled sensitivity and specificity of single-shot EPI DWI were 0.83 (95%CI: 0.79-0.87) and 0.77 (95%CI: 0.70-0.83), respectively. PLR and NLR were 5.09 (95%CI: 2.19-11.84) and 0.23 (95%CI: 0.15-0.36), respectively. The *P* value for the χ^2 heterogeneity for all pooled estimates was < 0.05 .

The overall accuracy was further explored by drawing SROC curves and finding the area under the curve (AUC) and *Q** index (Figure 3), which were 0.89 and 0.82, respectively, indicating good diagnostic

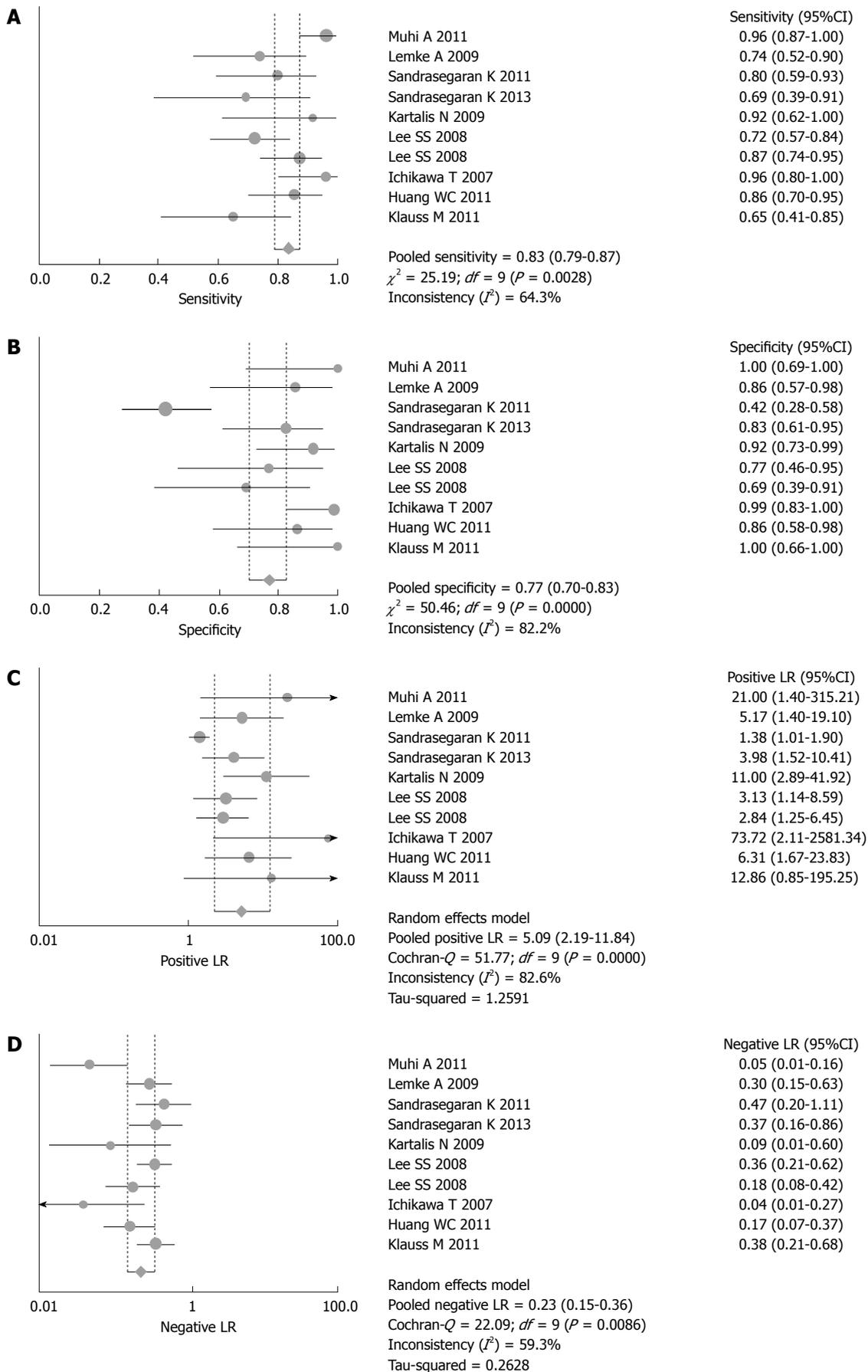


Figure 2 Forest plot of sensitivity (A), specificity (B), positive likelihood ratio (C) and negative likelihood ratio (D) with corresponding 95%CI of nine studies (10 sets of data). The random-effects model was used. The pooled sensitivity and specificity of DWI were 0.83 (95%CI: 0.79-0.87) and 0.77 (95%CI: 0.70-0.83), respectively. Positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were 5.09 (95%CI: 2.19-11.84) and 0.23 (95%CI: 0.15-0.36), respectively.

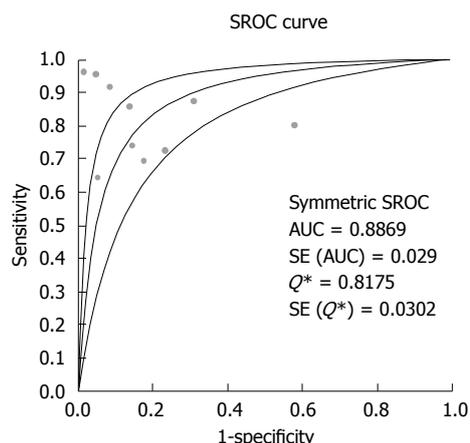


Figure 3 Summary receiver operating characteristic curve. Sensitivity and specificity are plotted in the receiver operating characteristic space for individual studies. The AUC and Q^* index were 0.89 and 0.82, respectively, indicating good diagnostic accuracy. SROC: Summary receiver operating characteristic.

accuracy.

Publication bias was not observed (Figure 4; $t = 0.58$, $P = 0.58$).

The meta-regression analysis indicated that fat suppression, mean age, TE, and maximum b factor were not sources of heterogeneity (all $P > 0.05$).

DISCUSSION

Research concerning pancreatic DWI is rapidly expanding, and a growing amount of data are being published^[5,16,24-28]. Fast imaging is important to avoid motion artifacts. The advantage of using single-shot EPI as a readout sequence is that only one excitation is necessary, and hence the DW images become less sensitive to subject motion^[9].

Based on calculations of the relevant data available in the currently published articles, our systematic review and meta-analysis demonstrated that pancreatic single-shot EPI DWI was useful to differentiate between malignant and benign pancreatic lesions. The pooled sensitivity and specificity were 83% and 77%, respectively. PLR and NLR were 5.09 and 0.23, respectively. From the fitted SROC, AUC was 0.89 and Q^* , the point where sensitivity equals specificity, was 0.82. All these data indicated that the overall diagnostic performance of single-shot EPI to differentiate malignant from benign pancreatic lesions was high.

There was significant heterogeneity among the studies in our analysis; therefore, it is critical to investigate the source of heterogeneity to determine the potential impact factors. Publication bias is a common source of heterogeneity in meta-analyses. However, in the present analysis, the funnel plot suggested that there may not have been publication bias. Meta-regression analysis was performed to explore other sources of heterogeneity for pancreatic DWI.

There are many factors that affect the signal

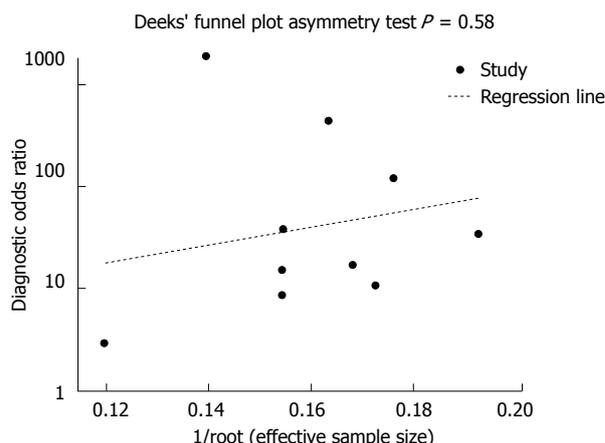


Figure 4 Publication bias was not present ($t = 0.58$, $P = 0.577$).

intensity on DWI and affect measured ADC values^[29-32]. Meta-regression analysis indicated that fat suppression, mean age, TE, and maximum b factor were not sources of heterogeneity. The best acquisition strategies for DWI data in the focal pancreatic disease are still a matter of debate. There was considerable variation in the results, which indicated that more-detailed, high-quality prospective studies on pancreatic DWI should be carried out to establish the presence of heterogeneity.

Some limitations of the present study should be mentioned. First, as described above, there was notable heterogeneity among the studies. Evaluated covariates were the sources of the heterogeneity, which requires further study. Standardization of the acquisition protocol for pancreatic DWI across the multicenter studies is recommended. Lesion size ≥ 2 cm was the limit for the diagnosis of early lesions. Optimization of the DWI protocol includes appropriate b-value selection, sufficient signal-to-noise ratio, adequate fat suppression, and artifact reduction via shimming and parallel imaging^[6]. The application of those techniques may be necessary to enhance the results of the present study.

In conclusion, single-shot EPI DWI was useful to differentiate between malignant and benign pancreatic lesions. The pooled sensitivity and specificity were 83% and 77%, respectively. PLR and NLR were 5.09 and 0.23, respectively. From the fitted SROC, AUC was 0.89 and Q^* was 0.82. Lesion size ≥ 2 cm was the limit for the diagnosis of early lesions. More-detailed, high-quality prospective studies on pancreatic DWI should be carried out to establish the presence of heterogeneity.

COMMENTS

Background

Diffusion-weighted imaging (DWI) provides tissue contrast based on the diffusion properties of water molecules in tissue, without using any contrast agents. The advantage of using single-shot echo-planar imaging (EPI) as a readout sequence is that only one excitation is necessary, and hence the DW

images become less sensitive to subject motion.

Research frontiers

There is no current consensus on the diagnostic ability of single-shot EPI DWI. We conducted a systematic review to investigate the diagnostic capability of single-shot EPI DWI to differentiate between malignant and benign pancreatic focal lesions.

Innovations and breakthroughs

Lesion size ≥ 2 cm was the limit for the diagnosis of early lesions. More detailed, high quality prospective studies on pancreatic DWI should be carried out in the presence of heterogeneity.

Applications

Single-shot EPI DWI was useful to differentiate between malignant and benign pancreatic focal lesions.

Terminology

DWI provides tissue contrast based on the diffusion properties of water molecules in tissue. DWI has a potential role in the differentiation and evaluation of pancreatic masses on the basis of the high contrast between the lesion and normal tissue.

Peer-review

The paper discusses the prognostic value of single-shot EPI DWI in differentiation of benign vs malignant pancreatic masses. The meta-analysis is comprehensive and carefully done.

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