



## The impact of tutor expertise on the students' scores in active learning methods: a meta-analysis

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### Abstract

**Introduction:** The tutor's role has been changing in the active learning methods in comparison to the traditional ones. Tutors are encouraged to become facilitators and to guide the students to construct a new knowledge by making bridges with the old one. Tutor's expertise in the active methods has been discussed with different results. The aim of this study was to assess the impact of tutor expertise on the students' scores in active learning methods.

**Methods:** The authors conducted this meta-analysis under the guidelines of a critical tool for systematic reviews (AMSTAR2). PubMed, Embase, Cochrane library, Scopus and Science Direct were the databases used for searching. The articles included compared students' learning scores according to tutor expertise between 2 groups of students with an active method of learning. The Review Manager software 5.3 was used to conduct this meta-analysis. We considered the mean difference as the effect size.

**Results:** 3169 students and 222 learning groups of 5 to 10 students were included in this study. The combined mean difference reached 0.84 with 95% CI [0.22, 1.46]. A significant difference between the two groups was observed in favour of the non-expert group (P=0.008). The heterogeneity I-square was evaluated to 98%. The Funnel plot reflected no publication bias (P=0.21). A sub-group analysis was performed taking into account the studies dealing with medical curriculum and the assessment methods used. It showed a significant difference between the two groups in favour of non-expert tutors (P<0.05).

**Conclusion:** Even if the results of this meta-analysis couldn't be conclusive and can't induce recommendations, they highlighted the tendency of non-expert tutors to be more student-centred. The heterogeneity observed can be decreased by establishing consensual definitions of expertise and assessment tools in further research studies in order to reflect the validity and efficiency of different tutoring styles in active learning methods.

**Keywords:** Learning, Problem-based learning, Lecture, Student

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Please cite this paper as:  
Mlika M, Majdi Zorgati  
M, Mezni F. The impact  
of tutor expertise on the  
students' scores in active  
learning methods: a  
meta-analysis. J Adv Med  
Educ Prof. 2022;10(4):235-  
245. DOI: 10.30476/  
JAMP.2022.94450.1589.

**Received:** 25 January 2022  
**Accepted:** 22 June 2022

### Introduction

Active learning methods based on realistic cases have been reported as more efficient methods than traditional lecture-based methods. These methods integrate the concept of a

student-centred-learning and make the student responsible for his learning, which is directed by educational objectives and competences. Students included in lecture-based courses were reported to be 1.5 times more likely to

fail in comparison to those included in case-based learning (1). Even if students have to be more self sufficient, the role of the tutor remains central and mandatory. The students are encouraged to have a large tutor network with different subjects of expertise. The tutors' roles in the active methods have been changing from a directive role to a facilitative and guiding role. The tutor can allow the learning process to flourish or crush. In traditional learning methods, the teacher teaches themes according to his subject of knowledge or research. On the other hand, the tutor in active learning methods may belong to the academic staff or may also be a pregraduate or a postgraduate student. As the role of the tutor has been changing in active methods, the tutor's expertise becomes more difficult to define or to approach (2, 3). The influence of the tutor's expertise on the students' learning has to be assessed and evaluated. Even if active methods, which consist mainly in case-based, team-based and problem-based learning, have largely been approved and adopted by university boards, many interrogations remain concerning the tutors' expertise needed. For that purpose, the authors tried to gather results of quantitative studies dealing with the assessment of the effect of the tutor's expertise on the students' learning and knowledge.

## Methods

- **Data source and search:** The authors conducted this meta-analysis under the guidelines of a critical tool for systematic reviews (AMSTAR2) (2). To retrieve all eligible articles, PubMed Embase databases, science direct, Scopus and Cochrane Library were comprehensively searched up to March 2022 in French and English languages. The search medical subject heading (MeSH) terms employed for literature retrieval in PubMed included: tutoring, case-based learning, problem-based learning, and team-based learning. The reference list of eligible articles was also independently searched by 2 authors to obtain other valuable sources.

- **Study selection criteria:** To be qualified for inclusion in this meta-analysis, the articles must comply with all of the following criteria: the authors have to use active learning methods comparing 2 groups of students with or without a randomization. Each group has to be tutored by tutors with different expertise levels. Besides, both groups' new knowledge has to be assessed using a quantitative assessment method (scores) and not a qualitative method such as a binary result. The definition of expertise which was

assumed by the authors, the method of scoring, and the number of students assessed must be cited. The major exclusion criteria were as follows: studies with duplicate data reported in other studies and reviews, technical reports, case reports, comments or letters with invalid data and qualitative or questionnaire-based studies.

- **Data extraction and Quality assessment:** One investigator (MM) independently reviewed all of the articles and extracted data from the selected articles: first authors' name, publication year, title, research question, type of study, synopsis, definition of expertise adopted by the authors, the active learning method used, the curriculum assessed, the evaluator, the scoring method used and the description of the learning scenario. In addition, based on the Medical Education Research Quality Instrument (MERQI) criteria for quantitative studies, the included articles were rated (3). The scoring criteria consisted of 6 items: the study design, the sampling, and the type of data, the validity of the evaluation instrument, the data analysis and the outcomes. The maximum score attributed was 18.

- **Statistical analysis:** The Review Manager software 5.3 was used to conduct this meta-analysis. The mean scores for every group of students, those tutored by an expert tutor and those tutored by a non-expert tutor, were assessed. The mean scores were used because of the similarity of the units used. For the expert and non-expert groups, the standard deviation, the number of students in the expert group and non-expert group with the 95% confidence intervals were recorded. A fixed model was adopted. We considered the mean difference as the effect size.

**Heterogeneity:** The Q test and I<sup>2</sup> statistics were carried out to explore the heterogeneity among studies. P value < 0.1 for the Q test or I<sup>2</sup> value > 50% represented substantial heterogeneity between studies. Besides, based on the characteristics of the included articles, a subgroup analysis was performed in order to explore the potential sources of heterogeneity if necessary.

**Publication bias:** In order to assess a potential publication bias, a funnel plot analysis and the Egger test were performed.

## Results

- **Search results:** Our database research retrieved 1259 records. For example, the MESH search using this equation: "tutor"[All Fields] OR "tutor's"[All Fields] OR "tutored"[All Fields] OR "tutoring"[All Fields] OR "tutors"[All Fields] OR ("case-based"[All Fields] AND ("learning"[MeSH Terms] OR "learning"[All

Fields] OR “learn”[All Fields] OR “learned”[All Fields] OR “learning’s”[All Fields] OR “learnings”[All Fields] OR “learns”[All Fields]) OR (“problem based learning”[MeSH Terms] OR (“problem based”[All Fields] AND “learning”[All Fields]) OR “problem based learning”[All Fields] OR (“problem”[All Fields] AND “based”[All Fields] AND “learning”[All Fields]) OR “problem based learning”[All Fields])) AND (“team-based”[All Fields] AND (“learning”[MeSH Terms] OR “learning”[All Fields] OR “learn”[All Fields] OR “learned”[All Fields] OR “learning”[All Fields] OR “learnings”[All Fields] OR “learns”[All Fields])) on pubmed, highlighted 527 manuscripts. This strategy was also employed using the other databases. After reviewing the titles and abstracts, 1226 records were excluded due to language limit and unrelated studies. By reviewing full-text articles, we excluded further 26 records, leaving 9 eligible articles. Chng E, et al. assessed the extent of tutor’s behaviors on student learning by comparing high social congruent tutors to lower ones, high cognitive congruent tutors to lower ones, subject-expert tutors to non-expert ones (4). Besides, they compared both groups’ performance according to the tutors’ congruence during different times of the problem-based learning: after problem analysis, after self-directed learning and after reporting. We considered the different subgroup analyses performed by Chng E, et al. as separate studies. Mathes, et al. studied the influence of tutor qualification on the process and outcome of learning in the problem-based course (5). They performed subgroup analyses. The first

subgroup was subdivided based on the pre or post graduation of the tutors and the second group was studied according to the tutor’s term experience in coaching. Because of these subdivisions, the study of Mathes, et al. was considered twice in our analysis. According to these criteria, this analysis included 15 studies. Figure 1 illustrates the flowchart of the literature review.

- **Descriptive results:** Study design: All studies compared the learning scores of 2 groups of students tutored by expert and non-expert tutors. Seven studies were controlled randomized studies (6-12). Eight studies were not randomized studies (4, 5). As mentioned in the search section, these studies were considered respectively twice and six times. The students were allocated to two groups by the Faculty Department and a randomization wasn’t possible. In the latter, the authors described a usual learning process in their universities and the university boards assigned the tutors to teach the students. The different groups were determined according to the tutors’ expertise as defined by the authors. Fourteen studies were quantitative and compared students’ scores in 2 groups. Sa, et al. reported a semi-quantitative study and we summed the different percentages reported in order to approach the students’ scores (9).

Medical Education Research Quality Instrument (MERQI) score: the mean MERQI score of the included studies was 14.16.

Curriculum assessed: Eight studies assessed a medical curriculum (5-8, 11, 12). The other studies didn’t concern a medical curriculum. According to the Flexner approach, 3 studies

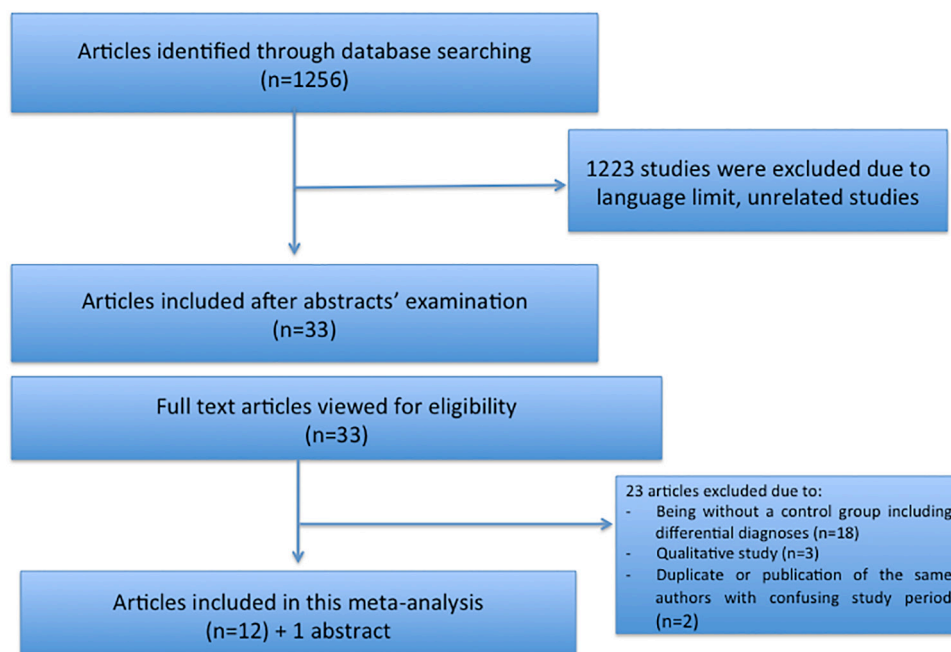


Figure 1: the flowchart showing the different steps of the literature review

concerned the preclinical years (first and second year) (6, 7, 11). The other studies concerned the second period of the Flexnerian curriculum (third and fourth year) (5, 8, 9). The assessment period lasted one year in 9 studies (4, 8, 9, 11), 6 months in 1 study (6), 2 years in 1 study (7), less than six months in 1 study (10), 4 years in 1 study (5) and 6 years in 1 study (12). The method of learning consisted of problem-based learning in all studies and was associated to a lecture-based learning in 1 study (10) and a case-based learning in 1 study (8). The learning scenario details were reported in 11 studies. The problem-based learning lasted a few hours in some studies or some days in others.

Expertise definition used: the definition of “expertise” varied in the different studies. Park, et al. based the expertise definition on the subject-qualification of the tutors (12). Other authors defined the tutor’s expertise based on their social congruence (4). Social congruence was defined as the empathy degree of the tutors and their adhesion degree to the difficulties and problems faced by the students. Cognitive congruence was also used by Chng, et al. in order to assess the tutors’ expertise. They defined the cognitive congruence of the tutors as their ability to deliver a clear and comprehensive message to students. In the study reported by Kaufman, et al., the expertise degree was self-assessed by the tutors based on the self-evaluation of their abilities to teach the material (7). Budé, et al. considered expert tutors those who were formed by the authors for the experience and included only subject-expert tutors (11). Gerhar, et al. subdivided the tutors into facilitative tutors and non-facilitative ones (10, 11). As tutors in case-based learning have a facilitative role, we considered the tutors with facilitative skills as expert ones for this kind of learning. Sa B, et al. subdivided the tutors according to their lenient and stringent potential (9). As tutors are considered to be the most lenient and the least stringent in the case-based learning process, we considered the group of lenient tutors as the expert group. Hay PJ, et al. considered expert tutors those who had previous experience in research, teaching and clinical training in the area of the problems analyzed by the students. Besides, all the tutors included in their studies were psychologists (8). Kim KJ, et al. considered expert tutors those who were staff tutors with a history of teaching (6). Mathes, et al. adopted 2 criteria to determine the expertise degree in their subgroup analyses: their teaching experience length for at least one term and the pre or post graduation degree (5), experts being senior staff tutors with completed post graduate experience and non-expert being

junior non-medical staff tutors (pharmacists, chemists...) and undergraduate medical students.

Assessment: The students’ assessment was performed immediately after the teaching period in all studies. Bude, et al. also assessed the impact of the learning process 6 months after the course (11).

The assessment method consisted of short questions and/or multiple-choice questions and/or short essay questions and/or quizzes in 7 studies (5, 6, 8-10, 12), open ended questions in 1 study (11), self-assessment by likert-scale questions in 1 study (7) and a published test (concept recall test) in 1 study (4).

Synopsis: No significant difference was reported between the two groups in 8 studies (4-7, 12). Significant results were observed in the expert tutored group in 5 studies (4, 8, 9, 11). Significant results were reported in the non-expert tutored group in 1 study (10). Chng E2 reported an influence of the tutor expertise based on the subject qualifications concerning average students (4). The scores of academically strong and weak students seemed not to be related to the subject expertise of the tutor. All of the results are represented in Table 1.

Meta-analysis results: 3169 students and 222 learning groups of 5 to 10 students were included in this study. The number of the tutors included was reported in 13 studies but not mentioned in 2 studies (5). The mean number of the tutors included was 35 (average ranging between 2 and 208). The combined mean difference reached 0.84 with 95% CI [0.22, 1.46]. A significant difference between both groups was observed in favour of the non-expert group ( $p=0.008$ ). The heterogeneity I-square was evaluated to 98% (Figure 2a). The Funnel plot reflected no publication bias and the eggers test revealed a  $p$  reaching 0.21 (Figure 2b).

Facing this important heterogeneity, we analysed the studies that evaluated a medical curriculum (5–8, 11, 12). The forest plot showed a significant difference between the two groups in favour of non-expert tutors ( $P<0.05$ ). On the other hand, the I-square accounted for 100% (Figure 3a). The comparison between both groups was also made based on the methods of assessment. We grouped all the studies that used multiple-choice questions and/or short questions and/or quizzes (5, 6, 8–12). The meta-analysis revealed a significant difference between students’ scores in favour of the non-expert tutors with I-square accounting for 100% (Figure 3b).

## Discussion

This meta-analysis highlighted the confusion present in the literature about the definition of tutors’ expertise in active learning methods. In

Table 1: the main characteristics of the articles included in the meta-analysis

Author	Year	Title	Research question	Type of study	Nbre students	Nbre tutors	Method of assessment	Synopsis	Definition of expertise	Learning method used	Learning scenario described	Curriculum evaluated	The evaluator	MER-QI Score :/18
Budé L, et al.	2011	The effect of directive tutor guidance on students' conceptual understanding of statistics in problem-based learning.	Would directive guidance improve the conceptual understanding of statistics in problem-based learning?	Control randomized	208	14	Open ended questions during the learning process and 6 months after the course for 24 students.	Providing directive tutor guidance improved understanding.	Intervention group: tutors with guidance Control group: All usual tutors. All tutors with content expertise.	PBL	Mentioned	First-year medical studies	Mot mentioned	13.5
Park SE, et al.	2007	Do tutor expertise and experience influence student performance in a problem-based curriculum?	Are tutor expertise and prior tutoring experience influencing student performance?	Control randomized trial	206	163 experts 43 non experts	Students' grades for the tutorial session, midterm examination and final examination.	Overall student performance in PBL is not affected by tutor expertise or prior tutoring experience.	Expert: tutor with specific background knowledge in the subject matter Non-expert: general dentists Prior tutoring experience: tutor who had been a PBL tutor for one year or more.	PBL	Not mentioned	Third-year dental students Between 2000-2005	The tutors	13.5
Gerhardt-Szep S, et al.	2016	Evaluating differently tutored groups in problem-based learning in a German dental curriculum: a mixed methods study.	How do the different tutoring styles (facilitative and nonfacilitative) affect learning motivation and success?	Randomized control study	106	4 trained with a 60-min seminar	Multiple-choice questions.	Non facilitative tuition resulted in a slightly larger knowledge gain (P=0.08).	Expert: facilitative tutor Non-expert: non facilitative tutor.	PBL with lectures	Mentioned	Summer term 2008 or 2009	The tutors	15
Sa B, et al. 2019	2019	Tutor assessment of PBL process: Does tutor variability affect objectivity and reliability?	To determine the extent of tutor variability in assessing the PBL process.	RCT	181	18: all used to PBL teaching	13 items covering 12 performance criteria and one global assessment.	The correlation between tutor's PBL experience and their mean ratings was moderately significant.	Expert: lenient tutors Non-expert: stringent tutors.	PBL	Not mentioned	Third-year bachelor medicine	The tutors	11.5

Chng E, et al.	2014	To what extent do tutor-related behaviours influence student learning in PBL?	To investigate the effect of tutor's social congruence on the students' learning process after problem analysis.	Non randomized trial	77	4	Concept recall test (Yew, et al. 2011).	Significant difference between students' score.	Expertise: social congruence.	PBL	Mentioned	Second year of study in poly-technic.	Tutors	15.5
Chng E, et al.	2014	To what extent do tutor-related behaviours influence student learning in PBL?	To investigate the effect of tutor's social congruence on the students' learning process after self-directed learning.	Non randomized trial	77	4	Concept recall test (Yew, et al. 2011).	No significant difference between both groups.	Expertise: social congruence.	PBL	mentioned	Second year of study in poly-technic.	Tutors	15.5
Chng E, et al.	2014	To what extent do tutor-related behaviours influence student learning in PBL?	To investigate the effect of tutor's social congruence on the students' learning process after reporting.	Non randomized trial	77	4	Concept recall test (Yew, et al. 2011).	No significant difference between both groups.	Expert: social congruence.	PBL	mentioned	Second year of study in poly-technic.	Tutors	15.5
Chng E, et al.	2014	To what extent do tutor-related behaviours influence student learning in PBL?	To investigate the effect of tutor's expertise on the students' learning process.	Non randomized trial	637	11	Concept recall test (Yew, et al. 2011).	Tutors' behaviours had a greater influence on average students as compared to the academically stronger and weaker students.	Expert: content skilled Non expert: non content skilled.	PBL	Mentioned	Second year of study in poly-technic.	Tutors	15.5

Chng E, et al.	2014	To what extent do tutor-related behaviours influence student learning in PBL?	To investigate the effect of tutor's social congruence on the students' learning process.	Non randomized trial	637	11	Concept recall test (Yew, et al. 2011).	Significant impact of social congruence.	Expert: social congruent Non-expert: non-social congruent.	PBL	Mentioned	Second year of study in poly-technic.	Tutors	15.5
Chng E, et al.	2014	To what extent do tutor-related behaviours influence student learning in PBL?	To investigate the effect of tutor's cognitive congruence on the students' learning process.	Non randomized trial	637	11	Concept recall test (Yew, et al. 2011).	No effect.	Expert: cognitive congruent Non expert: non cognitive congruent.	PBL	Mentioned	Second year of study in poly-technic.	Tutors	15.5
Hay PJ, et al.	2001	The expert in problem-based and case-based learning: necessary or not?	To compare expert and non-expert facilitated case-based and problem based teaching method.	RCT	118	2	Five short-answer questions.	Students taught by the expert scored higher in the end-of-course test.	Expert: practicing psychiatrist with previous experience in research, teaching and clinical training in the area of the problem Non expert: psychologist with no clinical training in the area of the problem, no previous experience of teaching or research in the area.	PBL and CBL	mentioned	Fourth year medical students.	Tutors	15.5
Kaufman DM, et al.	1998	The relationship of tutors' content expertise to interventions and perceptions in a PBL medical curriculum.	Do content expert tutors differ from nonexpert tutors in the extent to which they present or explain case content?	RCT	168	88	Self-assessment by Likert-scale questionnaires.	No difference between both groups.	Expertise determined by a self-rating of the tutors based on the following question: to what extent could you teach the material covered by the case.	PBL	mentioned	First two years of medical curriculum 1993/1994.	Tutors	8

Kim K, et al.	2009	General physicians graduated from a PBL undergraduate medical curriculum: how well do they perform as PBL tutors.	Effectiveness of PBL tutors.	RCT	40	76	Score including Quizzes+ peer evaluation + tutor evaluation + multiple-choice questions.	No significant difference.	Non expert: non staff tutors, graduates from the university with no experience in teaching Expert: staff tutors with a history of teaching.	PBL	Second year medical students: 6 months.	Not mentioned	13.5
Mattes J, et al.	2002	The influence of tutor qualification on the process and outcome of learning in a problem-based course of medical pharmacology.	To examine whether such use of non-expert and peer tutors as compared to expert tutors would harm learning outcome or the process of learning.	Non randomized trial	111 learning groups	-	Multiple-choice questions and short-essay questions.	No difference between the different groups concerning the exam results.	- Non expert and peers: junior staff tutors (physicians, pharmacists, veterinarians, biologists, chemists during postgraduate education) and undergraduate medical students >4th year - Expert: senior staff tutors (completed post graduate education).	PBL	4-year-prospective study with third year medical students.	Not mentioned	14.5
Mattes J, et al.	2002	The influence of tutor qualification on the process and outcome of learning in a problem-based course of medical pharmacology.	To examine the influence of tutor's teaching influence.	Non randomized trial	111 learning groups	-	Multiple-choice questions and short-essay questions.	No difference between the different groups concerning the exam results.	- Expert: tutors with at least one term experience in coaching PBL groups - Non expert: tutors without an experience of teaching.				



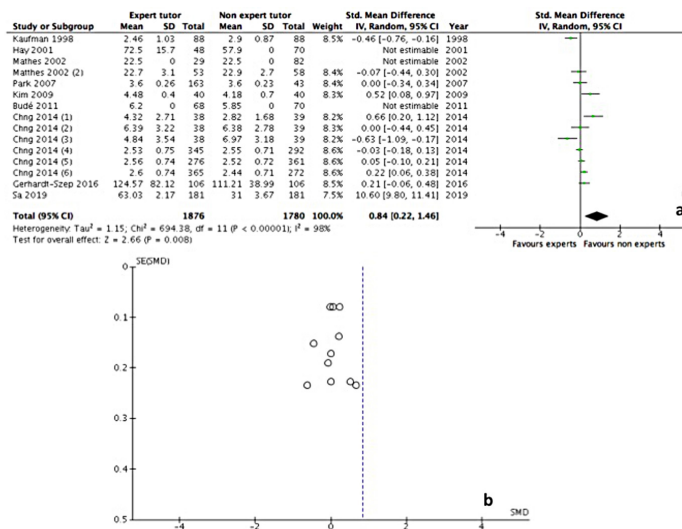


Figure 2: a/ Forest plots of the standard mean difference of the different articles included, b/ Funnel plot showing the absence of a publication bias

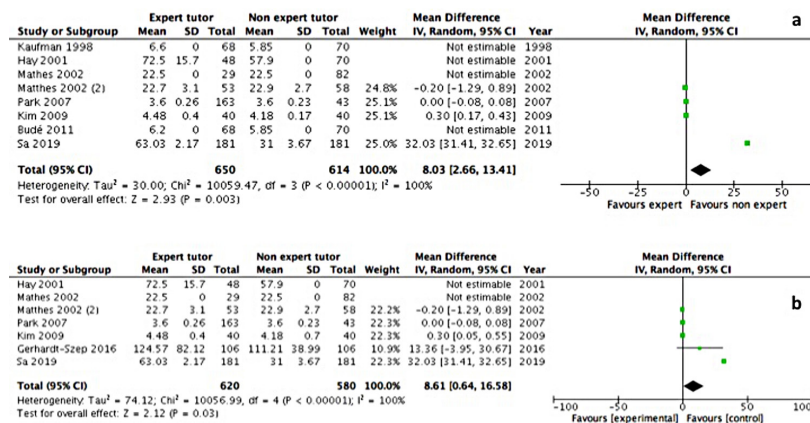


Figure 3: a/ Sub-group analysis including studies about medical curriculum showing the forest plots of the standard mean difference, b/ sub-group analysis including the studies using the same type of assessment tools showing the forest plots of the standard mean difference

fact, the definitions varied from qualification-based experience to teaching habits-based experience or graduation or social and cognitive congruence. Some authors have also established the tutor's expertise based on their self-perception (13). The confusion of the definitions could explain the importance of the heterogeneity in this study. In fact, even if this meta-analysis revealed results in favour of non-expert tutors in the main analysis and in the subgroup analyses, this result has to be taken with caution because of the multiple confounding factors. These factors include especially the variable expertise definitions, the different learning scenarios used, the different curricula assessed and the variable evaluation methods. The expertise definition is a real challenge in the literature. In a qualitative study about tutoring, Bochner D, et al. reported the preference of the students to expert tutors when expertise was defined by the tutor's previous tutorial experience. The authors

adopted a scoring system of the tutor expertise associating the educational degree, the subject expertise and the previous tutorial experience (12). In another qualitative study, Silver M, et al. reported the necessity of associating subject-matter knowledge and process-facilitation skills when dealing with case based learning (13). Perron NJ, et al. evaluated the quality of feedback during formative objective structured clinical encounters depending on the tutoring profile. They divided the tutors into generalists and specialists. They established that generalist tutors were more learner-centred and paid more attention to communication and professionalism during feedback than specialists (14). According to Jung B, et al. tutor expertise is based on their previous experience in tutoring. According to these authors, coaching of novice tutors has to be based on storytelling, demonstration and written material like manuals. The authors established a questionnaire-based study and reached the

conclusion of the necessity of putting emphasis on meeting and dialoguing between novice tutors and experienced ones, the availability of documented stories and the access to resource materials (15). Concerning the learning scenarios, even if the majority of the studies used problem-based learning, which was associated to case-based learning in one study and lectures in another study, the rare studies that described an accurate scenario adopted different schedules with the problem analysis steps lasting from few hours to few days. The case-based methods reported in the literature are variable and consist mainly of case-based learning, problem-based learning, team-based-learning and some modified methods (10, 12, 16-20). Many authors reported variable reactions of the students towards the methods used. Some authors reported the superiority of team-based learning (10, 16) and others advocate the efficiency of problem-based learning or case-based learning (21). Even if all these methods are based on an andragogical approach, some differences exist and consist of a prior individual work in team-based and case-based learning, an individual and team assessment in team-based learning and a peer evaluation in team based learning (22). These differences may induce variations in the motivation and satisfaction of the students. Moreover, no study presented the characteristics of the cases used. In fact, cases may be structured or unstructured. Structured cases give clear and specific identification of the disease in opposition to unstructured cases. Some authors reported that students preferred an unstructured approach to their cases (22-24). Besides, the self-directed learning period length varied between the different studies. This fact puts emphasis on the variety of the methods employed to perform a case-based-learning session. Some studies assessed students in the first two years of medical curriculum and other assessed students in the last two years of their medical curriculum. As the first two years characterize the pre-clinical Flexner period and the last years reflect the clinical Flexner period, the students may be not comparable concerning their knowledge and their self-accomplishment. In a satisfaction-study, Bochner D, et al. reported that the perception of the tutor's skills differ between the students according to their academic year (12). They highlighted that tutors were evaluated less favourably during the last academic years. The evaluation methods used were variable. Chng E, et al. were the only authors that adopted a published and consensual method (4). All these variations, which may be difficult to study, may explain the important heterogeneity noticed in

this study. The major limitations of this meta-analysis are the heterogeneity assessed, which wasn't explained by the different cofounding factors that were analysed. Besides, based on the inclusion criteria, the references were quite outdated. In fact, we chose the studies comparing quantitative variables concerning the students' new knowledge and the majority of the studies published were qualitative and questionnaire-based studies. We also, didn't perform a sensitivity analysis. As sensitivity analysis examines the effect of changing a single variable at a time and considering the fact that in every study included, some variables couldn't be controlled, we preferred to perform a sub-group analysis.

### Conclusion

Even if the results of this meta-analysis couldn't be conclusive and can't induce recommendations, they highlighted the tendency of non-expert tutors to be more student-centred. The important role of the tutor, as a facilitator, in active learning methods has been highlighted by some authors and under-recognized by others. Some authors have reported the possibility of replacing tutors by digital resources and described the advantages of tutorless problem-based learning. The heterogeneity observed can be decreased by establishing consensual definitions of expertise and assessment tools in further research studies in order to reflect the validity and efficiency of different tutoring styles in active learning methods.

### Authors' contribution

MM had the idea and performed the statistical analysis, MM, MZ and FM made the literature review, analysed the results and reviewed the manuscript. MM, MZ and FM red the final version manuscript and corrected it.

**Conflict of Interest:** None declared.

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