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Patients' perceptions on non-specific effects of acupuncture: Qualitative comparison between responders and non-responders

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ABSTRACT

Background: Non-specific effect of acupuncture constitutes part of the overall effect generated via clinical encounter beyond needle insertion and stimulation. It is unclear how responders and non-responders of acupuncture experience non-specific effects differently. We aimed to compare their experiences in a nested qualitative study embedded in an acupuncture randomized trial on functional dyspepsia.

Methods: Purposive sampling was used to capture experience of responders (n=15) and non-responders (n=15) to acupuncture via individual in-depth interviews. Design and analysis followed a framework analysis approach, with reference to an existing model on acupuncture non-specific effects. Themes emerging outside of this model were purposefully explored.

Results: Responders had a more trusting relationship with acupuncturist in response to their expression of empathy. In turn they were more actively engaged in lifestyle modifications and dietary advice offered by acupuncturists. Non-responders were not satisfied with the level of reassurance regarding acupuncture safety. They were also expecting more peer support from fellow participants, regarded that as an empowerment process for initiating and sustaining lifestyle changes.

Conclusions: Our results highlighted key differences in acupuncture non-specific effect components experienced by responders and non-responders. Positive non-specific effects contributing to overall benefits could be enhanced by emphasizing on empathy expression from acupuncturists, trust-building, offering appropriate explanations on safety, and organizing patient support groups. Further research on the relative importance of each component is warranted.

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1. Introduction

In recent decades, there has been increasing evidence from randomized controlled trials demonstrating that both acupuncture and sham acupuncture exert significant therapeutic effects on treatment outcomes when compared to no treatment.¹⁻⁵ While acupuncture has stronger effects than sham acupuncture,⁶ the dif-

ference between them is often smaller than that between sham acupuncture and no treatment.⁷ In a meta-analysis of randomized controlled trials comparing the effectiveness of acupuncture, sham acupuncture, and no acupuncture groups for alleviating pain,⁵ a small difference was observed between acupuncture and sham acupuncture (standardized mean difference: -0.17, 95% confidence interval: -0.26 to -0.08), while a moderate difference was observed between sham acupuncture and no acupuncture (standardized mean difference: -0.42, 95% confidence interval: -0.60 to -0.23). This implies that the impact of non-specific effect of acupuncture may play an important role on clinical care. The minor or insignificant differences found between

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Table 1
Definitions of key technical terms used in this qualitative study.

Key technical term	Definition
Specific effects of an intervention	The treatment effects are considered specific when they are solely attributable, in accordance with the theory of the mechanism of action, to the unique component of an intervention. ^{15,16}
Specific effects of acupuncture	The treatment effects of acupuncture are considered specific when they are solely attributable to needle insertion and manipulation at defined points. ^{7,15,19-21}
Specific effect components of an intervention	The specific effect components of an intervention are defined as the unique components which are causally responsible, in accordance with the theory of the mechanism of action, for the specific effects of an intervention. ^{15,16}
Specific effect components of acupuncture	Needle insertion and manipulation at defined points are considered as specific effect components of acupuncture as they are causally responsible for the specific effects of acupuncture. ^{7,15,19-21}
Non-specific effects of an intervention	Treatment effects are considered non-specific when they are associated with the incidental elements of an intervention. ⁷
Non-specific effects of acupuncture	The treatment effects of acupuncture are considered non-specific when they are induced by incidental elements of acupuncture other than needle insertion and manipulation at defined points. ^{7,22}
Non-specific effect components of an intervention	The non-specific effect components of an intervention are defined as the incidental elements which can induce treatment effects of an intervention, but they are not specified in the theory of the mechanism of action. ⁷
Non-specific effect components of acupuncture	The incidental elements of acupuncture other than needle insertion and manipulation at defined points are considered as non-specific effect components of acupuncture as they can induce treatment effect of acupuncture, but they are not specified in the theory of the mechanism of acupuncture needling. ^{7,22}
Positive non-specific effects of acupuncture	The non-specific treatment effects of acupuncture are considered positive when they lead to improvements on patient outcomes. ²⁴⁻²⁶
Negative non-specific effects of acupuncture	The non-specific treatment effects of acupuncture are considered negative when they cause deleterious effects on patient outcomes. ²⁵
Responders to treatment	Individuals who experience clinically significant changes in alleviation of symptoms from a treatment are considered as responders to that treatment. In the randomized trial where this qualitative study is embedded, responders to acupuncture treatment were those who indicated adequate relief of functional dyspepsia symptoms in a weekly binary question (i.e. yes) for $\geq 50\%$ over the 10-week follow-up period. ³⁰
Non-responders to treatment	Individuals who do not experience clinically significant changes in alleviation of symptoms from a treatment are considered as non-responders. In the randomized trial where this qualitative study is embedded, non-responders to acupuncture treatment were those who indicated adequate relief of functional dyspepsia symptoms in a weekly binary question (i.e. yes) for $< 50\%$ over the 10-week follow-up period. ³⁰
Model validity	Model validity, which is a subset to external validity, refers to the degree to which the conceptual model constructed by an experimental setting corresponds to the actual system in the real-life setting, in terms of etiology, setting, and practice characteristics. ⁷¹

acupuncture and sham acupuncture⁸⁻¹¹ may imply that sham acupuncture is associated with particularly potent non-specific effects.^{12,13}

Treatment effect of an intervention can be divided into specific and non-specific effects.¹⁴ The effects are considered specific when they are solely attributable, in accordance with the theory of the mechanism of action, to the unique component of an intervention.^{15,16} In contrast, the effects are considered non-specific when they are associated with the incidental elements of an intervention.⁷ Acupuncture is a complex intervention, including both specific and non-specific effects which contribute jointly to the total treatment effect.^{17,18} In acupuncture, the treatment effects solely attributable to needle insertion and manipulation at defined points are considered specific^{7,15,19-21} while the treatment effects resulted from incidental elements of acupuncture are considered non-specific.^{7,22} It has been showed that a broad combination of psychological, social, and environmental factors can influence non-specific effects of acupuncture, they may act alongside or interact with the specific effects of acupuncture (i.e. the treatment effects generated by needle insertion and manipulation at specific acupoints) to affect patient outcomes.²³ Definitions of key technical terms used in this study are shown in [Table 1](#).

The non-specific effects of an intervention, including acupuncture, could be positive or negative. When the non-specific effects lead to improvements on patient outcomes, they are considered positive.²⁴⁻²⁶ Oppositely, the non-specific effects are regarded as negative when they cause deleterious effects on patient outcomes.²⁵ These non-specific effects may be strategically elicited (for the positive ones) or prevented (for the negative ones) for improving the overall treatment effect of acupuncture, but it is uncertain how this could be achieved.

A recent systematic review synthesized qualitative evidence on four key non-specific effect components of acupuncture and sham

acupuncture,²⁷ namely: (i) patient's perception of the acupuncturist; (ii) patient's knowledge, attitudes, and behaviors; (iii) patient-acupuncturist relationship; and (iv) trial environment. All these four components may exert positive or negative non-specific effects on patients' treatment outcomes by affecting their responsiveness to acupuncture treatment. Whereas some individuals achieve clinically significant improvement symptoms from acupuncture treatment (i.e. responders to acupuncture treatment), others do not experience clinically relevant symptoms relief (i.e. non-responders to acupuncture treatment). Currently, it remains uncertain how these components influence the positive and negative non-specific effects of acupuncture in clinical trials, and subsequently how they will influence patients' responsiveness to the treatment. Knowledge on these mechanisms would facilitate the design of effective communication strategies which could maximize positive, while minimize negative, non-specific effects of acupuncture. Identifying and understanding the underlying mechanism of non-specific effects of acupuncture would be of great value for improving service quality and education for acupuncturists.

One strategy for exploring such mechanism is to compare and contrast experiences of responders and non-responders on acupuncture treatment in a clinical trial setting. The present study is a qualitative study nested in an acupuncture randomized controlled trial among patients with functional dyspepsia (FD). All participants in the acupuncture treatment group received the same treatment (i.e. real acupuncture), which means they exposed to the same specific effect components of acupuncture (i.e. needle insertion and manipulation at defined points). Among participants, some of them had clinically significant alleviation of FD symptoms (i.e. responders to acupuncture) while some did not (i.e. non-responders to acupuncture). We assumed that the main discrepancy in effectiveness between the two group participants is associated with different non-specific effects of acupuncture. We made

this assumption as a previous meta-analysis of trials has shown that 60% of the acupuncture effect is attributable to non-specific effect,⁶ implying that variation in size of non-specific effect experienced by patients would have a significant impact on treatment outcome. Meanwhile, in an empirical study where acupuncture's specific effect is absent, it is observed that size of acupuncture's non-specific effects can be strongly influenced by patients' perception and expectation.²⁸

We explored how responders and non-responders experienced non-specific effect components of acupuncture differently in this qualitative study, with an aim to provide a patient perspective on the key positive and negative non-specific effect components of acupuncture. Findings of this study may support the design of communication strategies that could elicit positive, while minimize negative, non-specific effects in acupuncture practice.

2. Methods

2.1. Overall trial design

This qualitative study was nested within an acupuncture randomized controlled trial conducted in Hong Kong, and the full trial protocol and full results was published separately.^{29,30} Briefly, this single-centre, pragmatic, randomized, parallel-group, superiority two-arm trial compared the effectiveness of (i) 20 sessions of electroacupuncture (EA) over 10 weeks plus on-demand gastrocaine with (ii) on-demand gastrocaine alone, in providing symptom relief and improved quality of life among 132 endoscopically confirmed, *H. pylori*-negative FD patients. EA is an acupuncture technique utilized with manual acupuncture, in which the needles are connected to an electric current after needle insertion at the chosen acupoints. This would produce synthetic impact of electric and needling stimulation.³¹ Acupuncturists followed the Hong Kong Centre for Health Protection practice benchmarks when performing acupuncture.³² Acupuncturists were allowed to answer any questions raised by participants regarding to functions and safety of acupuncture. Acupuncturists would give instructions related to lifestyle modifications and self-care advice based on Traditional Chinese Medicine theory when requested by participants.

The primary outcome was between-group difference in proportion of patients achieving adequate symptom relief at week 12. Following recommendations from the Rome III Design of Treatment Trials Committee,³³ participants were asked a weekly question on whether they had an adequate relief of FD symptoms (Yes / No) in the past seven days over a 10-week follow-up period, from week 3-12 of the intervention (week 1-2 were considered an 'induction period' for establishing treatment effect).³⁴ In this trial, treatment responders were defined as those responding "yes" \geq 50% over the 10-week period.³⁰ Conversely, non-responders were those answering "yes" $<$ 50% over the same period.³⁰ This trial was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CREC Reference number: 2014.552-T).

2.2. Qualitative study design and data collection

Purposive sampling method allows researchers to identify and select information-rich individuals who are knowledgeable about or experienced with a phenomenon of interest.^{35,36} In this trial, responders and non-responders had both completed acupuncture treatments offered, and it is expected that they have experienced non-specific effects of acupuncture differently. Hence, purposive sampling was applied to identify these two distinct groups, capturing their different experiences. We approached 30 patients who completed treatments in the EA group at the end of week 12 after the completion of quantitative data collection. Among them, 15

were responders and 15 non-responders based on their primary outcome. All patients were informed about the purpose of the interview, anonymity of their responses, and their right to refuse to participate. All 30 patients agreed to participate. After providing written informed consent, these 30 patients participated in a semi-structured, face-to-face, individual in-depth interview on their treatment experience. Interviews were conducted from April 2016 to May 2017 at the Integrative Medical Clinic, the Chinese University of Hong Kong. Each patient was interviewed for approximately 30 minutes. Interviews were conducted by a male PhD student who has experience in conducting qualitative research. The interviewer (RH) was independent from the operation of the clinical trial, and he has no prior relationships with the participants. The participants did not know the personal goals of the interviewer; however, they were educated about the scientific reasons for doing this interview during the informed consent process. No other person was present in the interview besides the participants and the interviewer.

We used the saturation principle for guiding sample size estimation for this qualitative study.³⁷ Literature suggests that a sample size of 10 to 13 interviews would be adequate to achieve data saturation.³⁸ Based on our iterative analysis of the data, we determined saturation had been reached after 15 responders and 15 non-responders were interviewed and no new information was discovered from about the 12th interviews onward. Interviews were audio-recorded, transcribed verbatim by a person independent to the study, and were imported into NVivo 11 software for analysis. Pre-specified questions for the interview were prepared by RH and critical comments were provided by VC (Table 2). Transcripts were not returned to participants.

Reflexivity has been recognized as an essential strategy in qualitative research.³⁹ By turning the lens back onto ourselves as investigators, we can self-evaluate and recognize our situatedness within the study and the impact that it might have on the research process.^{40,41} As investigators devoted to patient centered development of integrative medicine, we explicitly acknowledged our positive attitude towards maximizing the non-specific effect of acupuncture for patients' benefit. Based on our current research knowledge and clinical experience, we assumed that some uninvestigated components, beyond needle insertion and stimulation, influence both positive and negative non-specific effects of acupuncture. These in turn influence patients' responsiveness to treatment in both trial settings and routine clinical practice. Being aware of our subjectivity in this research topic, we adopted different strategies to lessen its potential impact at different stages of the study. For example, the interviewer, who is not an acupuncturist, tried to elicit interviewees' experience by asking open-ended questions, using appropriate probes and applying active listening skills. He conscientiously avoided imposing his thoughts on this topic toward the patients during the interviews. Moreover, before starting a new interview, the interviewer listened to recording of the previous interview to locate information gaps, and he would discuss with other team members on the interim analysis results. Through this iterative data collection and analysis cycles, he could reflect on how his own positioning and presence shaped conversations with interviewees. He can then improve his interviewing skills continuously, ensuring both "quality" and "quantity" of data generated from interview conversations. Investigators' involvement in the study and its potential or actual effect upon the findings were monitored, and these measured maintained credibility and accuracy of the findings.⁴²

2.3. Data analysis

We applied the framework analysis approach,⁴³ with reference to a conceptual framework on non-specific effects components of

Table 2
Pre-specified interview questions for responders and non-responders to acupuncture.

Interview question	Relevant domains and themes from the reference model ²⁷ from which the question originated
1. Do your symptoms of functional dyspepsia change after completing acupuncture treatment? Do you feel better or worse due to the lifestyle changes that you made? Please share your experience with us.	Domain: Patient's knowledge, attitudes, and behaviors Theme: The patient's holistic understanding of his or her own medical conditions Confidence in the ability to control one's own health Ability to adapt behaviors based on experiences in the clinical trial
2. How does acupuncture affect your appetite and mood?	Domain: Patient's knowledge, attitudes, and behaviors Theme: The patient's holistic understanding of his or her own medical conditions Confidence in the ability to control one's own health Ability to adapt behaviors based on experiences in the clinical trial
3. Do you think the questions we asked you in the outcome assessment are comprehensive enough for evaluating the effect of acupuncture? Please elaborate.	Domain: Patient's knowledge, attitudes, and behaviors Theme: The patient's holistic understanding of his or her own medical conditions Ability to adapt behaviors based on experiences in the clinical trial
4. What do you think about our acupuncturists with regards to their professionalism, skills and interactions with you?	Domain: Patient's perception of the acupuncturist Theme: Holistic treatment approach Professional status
5. Would you prefer the acupuncturists to talk to you more? For example, offering you more lifestyle advices? Do you talk to acupuncturists actively? Why and why not?	Domain: Patient-acupuncturist relationship Theme: Trust
6. Do you learn anything useful or new upon joining our trial?	Domain: Patient's knowledge, attitudes, and behaviors Theme: Active engagement with acupuncturists
7. What motivates you to join our trial? Were you concerned about the potential negative effects?	Domain: Patient's knowledge, attitudes, and behaviors Theme: The patient's holistic understanding of his or her own medical conditions Ability to adapt behaviors based on experiences in the clinical trial
8. Do you have any other positive or negative experiences or suggestion that you would like to share?	Domain: Patient's knowledge, attitudes, and behaviors Theme: Positive attitudes and expectations Domain: Patient's perception of the acupuncturist Theme: Holistic treatment approach Acupuncturist's explanation regarding the theory of acupuncture and sham acupuncture
	Domain: Patient's knowledge, attitudes, and behaviors Theme: Confidence in the ability to control one's own health Positive attitudes and expectations Ability to adapt behaviors based on experiences in the clinical trial Domain: Trial environment Theme: Pleasant trial environment Trial design

acupuncture developed in a recent systematic review.²⁷ These non-specific effect components were developed from a meta-synthesis of qualitative findings derived from acupuncture trial settings;²⁷ providing a relevant starting point for investigating differential experiences of non-specific effect amongst our responders and non-responders. In the analysis we expanded beyond this model, and purposefully explored potential new insights. A list of non-specific effect components described in this framework is shown in Table 3, and this is referred to as the “reference model” hereafter.

Specifically, data analysis was conducted in 7 steps. (1) One researcher (RH) gained an overview of the dialogue content. (2) Segments of transcripts corresponding to the particular theme of the reference model were systematically coded using NVivo 11 software. (3) Coded themes that were similar across responders and non-responders were grouped; followed by (4) stratification of coded themes that were different between responders and non-responders. (5) Emerging new themes that were not explained by the reference model were also identified from the transcripts. (6) At this stage, we stratified the themes into “experienced” and “expected” topics, of which the later are expected but not experienced by the patients. (7) Finally, commonalities and differences of non-specific effects experienced by responders and non-responders were illustrated in the format of a schematic diagram.

In addition to the reflexivity strategy mentioned earlier, we also adopted different triangulation strategies to secure findings' trustworthiness. Data source triangulation was realized by exploring treatment experience of both responders and non-responders. Data obtained from multiple perspectives helped us to develop a comprehensive understanding on patients' experience of non-specific effects of acupuncture.⁴⁴ Moreover, two independent analysts engaged in the data coding and analysis process. After the first analyst (RH) completed transcript coding, a second analyst (CW) independently assessed the codes. Once a discrepancy appears, consensus would be sought from a third analyst (VC). Through repeated cycles of discussion, re-reading transcripts, and reflection, investigator triangulation provided multiple observations and conclusions from different investigators' perspectives, and strengthened trustworthiness of findings.⁴⁵ Guided by this iterative data analytic process, an enriched framework for enhancing key components of non-specific effect of acupuncture was generated.

3. Results

Characteristics of responders and non-responders participating the interview are shown in Table 4. The quantitative characteristics between responders and non-responders regarding their

Table 3
Reference model of non-specific effect components of acupuncture and sham acupuncture.²⁷

Domain	Non-specific effect components and their descriptions of acupuncture and sham acupuncture
Patient's perceptions of the acupuncturist	1.1 Holistic treatment approach <ul style="list-style-type: none"> • Acupuncturists do not just focus on a single condition, but rather treat patients with multiple conditions in a holistic manner.
	1.2 The acupuncturists' explanation regarding the theory of acupuncture and sham acupuncture <ul style="list-style-type: none"> • Patients benefit from the acupuncturist's explanation of the mechanisms underlying the effects of treatment.
	1.3 Professional status <ul style="list-style-type: none"> • Patients tend to have higher expectations regarding the success of treatment when acupuncturists maintain a professional status, authority, and expertise in their field.
	2.1 The patient's holistic understanding of his or her own medical conditions <ul style="list-style-type: none"> • Access to knowledge provided by acupuncturists increases the ability of patients to understand and manage their own medical conditions in a holistic manner.
Patient's knowledge, attitudes, and behaviors	2.2 Confidence in the ability to control one's own health <ul style="list-style-type: none"> • As acupuncture treatment progress, patients gain confidence in their ability to cope with their own medical conditions.
	2.3 Positive attitudes and expectations <ul style="list-style-type: none"> • Having a positive attitude and high expectations regarding treatment efficacy can lead to positive health outcomes.
	2.4 Active engagement with acupuncturists <ul style="list-style-type: none"> • Active patient engagement increases the likelihood to experience health benefits.
	2.5 Ability to adapt behaviors based on experiences in the clinical trial <ul style="list-style-type: none"> • Over the course of treatment, patients are more willing to make behavioral modifications, which may increase the efficacy of treatment.
	3.1 Trust <ul style="list-style-type: none"> • Trust between the patient and acupuncturist is the fundamental building block for the development of a healthy patient-acupuncturist relationship and is necessary for the formation of a strong therapeutic alliance.
Patient-acupuncturist relationship	3.1 Trust <ul style="list-style-type: none"> • Trust between the patient and acupuncturist is the fundamental building block for the development of a healthy patient-acupuncturist relationship and is necessary for the formation of a strong therapeutic alliance.
Trial environment	4.1 Pleasant trial environment <ul style="list-style-type: none"> • Sufficient consultation time as well as a supportive, calm, relaxing, and friendly environment is essential for positive patient experience.
	4.2 Trial design <ul style="list-style-type: none"> • Appropriate data collection procedures and attentive interviewers appear to be associated with positive treatment outcomes.

FD symptom severity, disease duration, and expectation about EA treatment measured by Stanford Expectations of Treatment Scale⁴⁶ were shown in Table 5. All the aforementioned characteristics were shown to be insignificant between two groups except for the expected differences in symptom severity.

Commonalities and differences of experiences and expectations of non-specific effects among responders and non-responders are illustrated in Fig. 1. These details are reported below.

3.1. Non-specific effect components of acupuncture experienced and expected by **both** responders and non-responders

3.1.1. Professional qualifications of acupuncturists

In this trial, all acupuncture treatment was provided by Chinese medicine practitioners (CMPs) registered with the Chinese Medicine Council of Hong Kong.⁴⁷ Both responders and non-responders preferred acupuncture to be provided by fully registered practitioners in a University setting and perceived this a key source of confidence on their acupuncturists' competence. "I place

more confidence in the acupuncturists if they are working for the University or the public sector, rather than acupuncturists with no such affiliations. I would not consider the latter as there are no guarantee on their competence." (035, responder). "if I were to choose an acupuncturist, I would choose those who have a University or public sector affiliation. This signals that they are better than acupuncturists with no institutional affiliations." (050, non-responder).

3.1.2. Avoidance of side effects from conventional medications

Upon experiencing acupuncture in the trial, participants viewed acupuncture as an alternative to conventional medication, or as a way to reduce conventional medication-associated side effects. "I think receiving acupuncture is a good thing as I can take reduce my long-term medication intake and subsequently experience less side effects from them." (004, responder). For non-responders, even their magnitude of improvement was smaller, being able to avoid side effects from conventional medications were still regarded as a benefit. "I know that I cannot fully recover from FD within a short period of time, but long-term medication is causing substantial adverse ef-

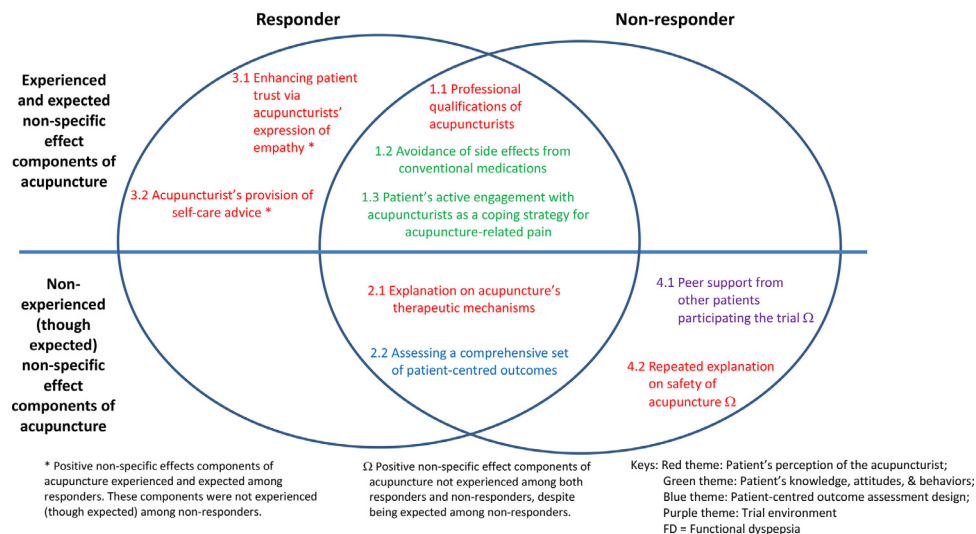


Fig. 1. Commonalities and Differences of Non-specific Effect Components Experienced by Responders and Non-responders.

Table 4
Characteristics between responders and non-responders to acupuncture participating the interview.

Item	Responder (n=15)	Non-responder (n=15)
Mean of age (SD)	51.9 (6.0)	45.7 (12.8)
Female, n (%)	12 (80.0)	10 (66.7)
Education level, n (%)		
Junior high school	1 (6.7)	2 (13.3)
High school	5 (33.3)	6 (40.0)
College	3 (20.0)	0 (0.0)
Vocational training	1 (6.7)	0 (0.0)
Degree	2 (13.3)	2 (13.3)
Degree or above	3 (20.0)	5 (33.3)
Marital status, n (%)		
Single	1 (6.7)	9 (60.0)
Married	12 (80.0)	6 (40.0)
Divorced	1 (6.7)	0 (0.0)
Widow	1 (6.7)	0 (0.0)
Employed, n (%)		
Retired	1 (6.7)	0 (0.0)
Unemployed	1 (6.7)	2 (13.3)
Housewife	2 (13.3)	3 (20.0)
Employed	11 (73.3)	10 (66.7)

SD, standard deviation.

fects. Acupuncture is an alternative to long-term medication like proton pump inhibitors.” (085, non-responder).

3.1.3. Patients' active engagement with acupuncturists as a coping strategy for acupuncture-related pain

Patients considered acupuncture-related pain as a negative non-specific effect, which lowered their commitment to the treatment.

To overcome or reduce pain during needle insertion, both responders and non-responders actively communicated and cooperated with their acupuncturists during the procedure, so as to minimize pain associated with the procedure. “I actively talk to my acupuncturists when they perform the procedure, so as to reduce my fear of pain. Talking can distract my focus from it.” (014, responder). It is acknowledged that needling pain could not be entirely eliminated; however, it might be reduced if patients discuss with their acupuncturists how to perform the procedure with minimal level of pain. “I requested my acupuncturists to needling certain acupuncture points very gently, because I cannot stand the pain...” (050, non-responder).

3.2. Non-specific effect components of acupuncture not experienced (though expected) by both responders and non-responders

3.2.1. Explanation on acupuncture's therapeutic mechanisms

Patients regarded explanations on acupuncture's therapeutic mechanism as a major source of positive non-specific effects. Such knowledge may increase a patient's confidence, as well as their commitment to completing the whole course of treatment. However, both responders and non-responders felt the explanations they received were insufficient, particularly in the following aspects: (i) rationale for choosing each acupuncture point; and (ii) function of each acupuncture point. For instance, patients suggested the acupuncturists should provide information on which acupuncture points were responsible for improving digestive function, sleeping quality, and general well-being, respectively. “I think my acupuncturists should provide rationale on why these acupuncture points were selected, as well as their function. In one session my

Table 5
Comparison between responders and non-responders participated in the interviews.

	Responder (n=15)	Non-responder (n=15)	P-values*
Mean duration of FD in years (SD)	11.8 (12.9)	8.6 (6.1)	0.39
Overall FD symptom severity score at Week 12# (SD)	2.3 (2.0)	4.8 (2.3)	0.004
Expectation to EA according to SETS` (SD)	22.3 (4.4)	23.2 (5.9)	0.63

FD, Functional Dyspepsia; SD, Standard deviation; EA, electroacupuncture; SETS, Stanford Expectations of Treatment Scale.

* P-values were generated from independent samples T test with equal variances assumed

Overall FD symptom severity score is calculated based on summation of individual symptom scores for assessing postprandial fullness, early satiety, epigastric pain, epigastric burning, and postprandial nausea (Rated on 5-point Likert scales, range: 0-20, the higher the score means the more severe the symptoms).

^ Range: 6-42, lower score indicates higher expectation on acupuncture treatment.

acupuncturist explained to me that some acupuncture points can help to improve my sleep quality or general health. I prefer the acupuncturists to explain the therapeutic mechanisms of acupuncture to me.” (017, responder). “My acupuncturists should explain more about how and why treatment on these acupuncture points would generate beneficial effects, as I don’t quite understand it.” (009, non-responder).

3.2.2. Assessing a comprehensive set of patient-centred outcomes

Instruments on FD symptoms, depression (9-item Patient Health Questionnaire), anxiety (7-item Generalized Anxiety Disorder Scale), and disease-specific quality of life (Nepean Dyspepsia Index) were included as trial outcomes. However, patients regarded these questions as insufficient in measuring their changes in diet, appetite and mood, particularly in exploring the relationships between these three factors. They desired understanding of these relationships, as such knowledge is considered to be keys for formulating tailored self-management strategies.

“What kind of food you eat might affect your fullness sensation and pain. Everybody’s stomach is different, as well as the causes of stomach pain – the reasons might be different among different people. I think you guys should understand more on the reasons on what the triggers are. We will know more about that if more questions are added into the assessment.” (050, non-responder). “I think more questions can be added to explore the relationship between appetite and mood, I think they are related to each other. I need to understand their relationship, so I know how to manage it myself” (009, non-responder).

3.3. Non-specific effect components of acupuncture **only** experienced and expected by responders

3.3.1. Enhancing patient trust via acupuncturists’ expression of empathy

Patients valued the expression of empathy from their acupuncturists, regarding this as a foundation for developing a trusting patient-acupuncturist relationship. While responders seem to benefit from such positive non-specific effect, empathy was not adequately experienced among non-responders, due to perceived inadequacy in the acupuncturists’ communication skills. “I feel happy and comfortable every time when I see and talk to my acupuncturists, as they expressed concern about myself and my family.” (002, responder). “In one session, I was having a flu, so I was not sure if I could receive acupuncture treatment that day. Unfortunately, that acupuncturist did not ask me anything about my flu and did not tell me whether I could still receive the treatment. It would be better if the acupuncturists can give me some assurance before performing acupuncture. Also, I would like my acupuncturists to tell me more about my treatment progress, not just inserting the needles into my body and leave the room.” (055, non-responder).

3.3.2. Acupuncturist’s provision of self-care advice

Patients expected that the acupuncturists would explain the causes of FD to them. These explanations were considered as an empowering tool for them to engage in symptom alleviating lifestyle modifications, and subsequently enhancing positive non-specific effect. Both responders and non-responders actively shared their own lifestyle habits to their acupuncturists, with an aim for a feedback on which habits would be beneficial or harmful to their symptoms. “When I come to an acupuncture session, I like to talk to my acupuncturists about the diet I was having. From this conversation, I learnt that I must adhere to a “clean” diet and stay away from spicy food.” (006, responder). “By talking to my acupuncturist, I want to know if my irregular dietary habit is a cause of FD, and if so, how should I change my eating habit accordingly.” (031, non-responder).

Responders mentioned that their acupuncturists had provided valuable self-care advice to them, which allowed them to modify

their lifestyle. This was thought to contribute to the alleviation of FD symptoms. However, non-responders felt that they did not acquire adequate self-care advice from their acupuncturists, and thus they could not make relevant lifestyle changes. Consistent with current knowledge on dietary habit as a key trigger of FD symptoms, dietary modification advice was considered as a key component of positive non-specific effect. “Acupuncturists have given me very useful lifestyle advice, including the avoidance of certain food. I think these helped me to alleviate symptoms, like fullness.” (014, responder). “I like to receive more self-care advice from my acupuncturist, things that I can do outside of the acupuncture sessions... like massaging certain acupuncture points or teaching me some dietary modification and exercise that would help with my digestion.” (050, non-responder).

3.4. Non-specific effect components of acupuncture **not** experienced (though expected) by non-responders

3.4.1. Peer support from other patients participating the trial

While most of the themes identified in the current qualitative study were consistent with the reference model, a newly emerging theme emerged: peer support from other trial participants as a potential non-specific effect component of acupuncture. Interestingly, only non-responders to acupuncture expressed desire to gain support from other participants, although it was not experienced due to the setup of the trial. Sharing of positive acupuncture experience with other patients with a similar condition were perceived as a potentially important source of positive non-specific effect among non-responders. Also, peer support was also regarded as an empowerment for initiating and sustaining lifestyle changes. Non-responders expected that they would be able to interact and learn from other patients on how they made changes successfully, which would have helped in reducing symptoms. “I would like to have other patients from the trial to give me some feedback regarding how acupuncture has helped them. It might be useful for me to learn from them, if certain lifestyle changes can help in alleviating the symptoms, and how to achieve that change.” (097, non-responder). Such new finding may inspire future research on how peer interaction may enhance positive non-specific effects of acupuncture.

3.4.2. Repeated explanation on safety of acupuncture

While the risks of acupuncture were fully explained to participants during the informed consent process by a registered CMP, non-responders expected that such explanation would be repeated in each session. Non-responders perceived that safety-related explanation as inadequate, and they were concerned that needle insertion would cause harm. Constant reassurance on the safety of acupuncture appeared to be a prerequisite for experiencing treatment benefit. “I want to know more about the safety of acupuncture. For example, would needling damage my nerves, organs, skin and muscle? I have received 20 acupuncture sessions in this trial; it’s quite a lot of sessions. I have constant concern on the safety issue.” (085, non-responder).

4. Discussion

4.1. Distinction between responders and non-responders

This qualitative study highlights differential experiences and expectations between responders and non-responders regarding their acupuncture treatment in a trial setting. Responders reported that acupuncturists’ expression of empathy enhanced the establishment of trust between them (Point 3.1, Fig. 1). Some previous studies suggested that empathy is important for generating the non-specific effects of sham acupuncture.⁴⁸ When acupuncturists are empathetic on patients’ needs, it allows the formation of a strong

patient-clinician relationship,⁴⁹⁻⁵³ fostering stronger trust on the acupuncturist. The association between higher trust and better outcome is known to be mediated via increased level of oxytocin. This increment is found to improve patients' overall health status and satisfaction.^{54,55} A strong patient-clinician relationship may have also facilitated patients' active engagement and compliance to acupuncturists' advice on dietary adjustment, subsequently leading to improvement on patient outcomes (Point 3.2, Fig. 1). Dietary adjustment is one of the dominating self care strategies in FD as existing literature reported that an irregular dietary patterns (e.g. skipping or eating extra meals), and consumption of sweet, fried and fatty food, as well as alcohol may give rise to symptom induction or exacerbation.^{56,57}

Our results suggested that non-responders did not expect nor experience the positive non-specific effect components described above. Instead, they expected constant reassurance on the safety of acupuncture, regarding the explanations provided by the acupuncturists as insufficient (Point 4.2, Fig. 1). In this trial, all participants were offered a standardized explanation on the low risk of harm from acupuncture by a registered CMP,⁵⁸ prior to the provision of informed consent to join the trial. While it is expected that such reassurance would reduce patients' anxiety,⁵⁹ it seems that the non-responders were not satisfied with the explanation. Perhaps detailed information provision on potential side effects of acupuncture contributes to their negative expectation and lack of trust,⁶⁰ thus lowering their experience of positive non-specific effects. Mechanistically, this untrustworthiness induced by uncertainty on safety may increase amygdala activity, and subsequently induce negative emotions.⁵⁴ In the future, constructing and testing an ethically appropriate communication method that minimizes negative non-specific effects of acupuncture is needed.⁶¹

4.2. Commonalities between responders and non-responders

Avoidance of adverse events from conventional medications was cited by participants as a major benefit of joining this trial.⁶² Both responders and non-responders suggested that the acupuncturists' professional qualification, as well as their affiliation with the University, contributes to their confidence on the treatment. A previous functional magnetic resonance study has shown that admiration for others may trigger activity of the posteromedial cortex, which associates with a sense of heightened awareness of self-condition and reassessment on one's own condition.⁶³ In our case, participants' admiration for acupuncturists' professional qualifications and their University affiliation is found beneficial to trust building. However, our findings did not show that whether such admiration could initiate a deeper reflection on patients' own medical conditions, and this association will need to be investigated in the future.

While pain minimization during treatment is considered an important competence of a good acupuncturist, both responders and non-responders agreed that pain from needle insertion cannot be eliminated. They actively communicated and interacted with acupuncturists during the treatment so as to reduce the pain associated with needle insertion. The perceived pain reduction may be achieved by (i) lowering negative expectation of the treatment, including anxiety and stress; (ii) gaining a sense of control and ownership in the process, and therefore increasing positive expectation on the treatment outcomes.⁶⁴ The benefits of such active coping style maybe mediated via lowering of cortisol levels during treatment.⁶⁵ While it is difficult to tell who initiates the engagement first in a good patient-clinician relationship, active encouragement from clinicians would be beneficial. Indeed, patient engagement is recently considered as a main strategy for increasing positive health outcomes in all types of medical treatments.⁶⁶

In the informed consent process, potential participants were provided with existing evidence from trials and systematic reviews on the potential effectiveness of acupuncture for FD, as well as its uncertainty, by a registered CMP. Despite the provision of clinical evidence, both responders and non-responders deemed such information as insufficient. Further mechanistic details of acupuncture from the perspective of both biomedicine and Chinese medicine (CM) were desired. There is a dearth of research on how different types of evidence provision (population- vs. basic science- vs. tradition CM theory-based) may impact the non-specific effects of acupuncture and patient outcomes.⁶⁷ Patients' understanding on each type of these explanations, and their corresponding influences on the confidence on CM modalities, including acupuncture, require further exploration.

4.3. Limitations of this study

Four major limitations of the study, resulting from the trial design, have been identified. Firstly, given the high prevalence of CM service use in the Hong Kong population,⁶⁸ majority of trial participants had previous experience of consulting a CMP. In routine practice, CM consultation entails four diagnoses (i.e. inquiry, inspection, listening, and palpation), followed by an individualized treatment plan, and subsequent treatment adjustment based on changes in patient's symptoms at each follow-up.⁶⁹ However, instead of implementing these typical CM consultation procedures, a fixed acupuncture treatment plan was administered to all trial participants to ensure the treatment fidelity. Discrepancy in CM diagnosis and treatment procedure between the trial setting and the real-world clinical practice may negatively affect the model validity.⁷⁰ As a subset to external validity, model validity refers to the degree to which the conceptual model constructed by an experimental setting corresponds to the actual system in the real-life setting, in terms of setting and practice characteristics.⁷¹

The lack of model validity may lower the strength of treatment effect. It is possible that patient may perceive the four CM diagnoses as sensory cues prior to acupuncture treatment, and the lack of these cues in the trial may hamper positive expectations on the treatment effects among patients.⁶⁴ Patients often perceive CM as holistic and patient-centred, acupuncture treatment without the four typical CM diagnostic components and a subsequent tailoring of treatment plan may contradict such patient expectation.⁷² Patients might think that they were not receiving authentic CM service, hence generating negative expectations on the treatment effect delivered in the trial context.⁶⁰ However, a randomized controlled trial has found that virtually no differences in efficacy between standardized and individualized acupuncture in pain management.⁷³ How individualized and standardized acupuncture may influence outcome could not be explored in this study as both responders and non-responders were received standardized treatment. Whether the nature of acupuncture treatment (i.e. individualized or standardized) has impacts on its non-specific effects, and how the impact differs among real and sham acupuncture remain to be uncertain. Answering this question is likely to be difficult as randomized trials without a reproducible acupuncture treatment protocol has limited generalizability,⁷⁴ and subsequently trials with such design are less likely to be funded. Also, design of trials preserving features of Chinese medicine is proven to be difficult due to the lack of reliable and valid Chinese medicine diagnostic instruments.^{75,76}

The second limitation originating from the trial design is that how peer support among patients influence non-specific effects of acupuncture could not be investigated, as participants were all offered with individual rather than group-based treatment. While non-responders expressed desire for peer support from other participants (Point 4.1, Fig. 1), this is not expected among respon-

ders. A previous study on group-based acupuncture suggests that peer support during treatment sessions yielded encouragement and comfort among participants.⁷⁷ Also, such interactions allowed responders to share their experiences to others, generating higher expectations on the positive non-specific effects of acupuncture.⁶⁴ Future acupuncture clinical trials and services may consider facilitating interactions and enhancing mutual help among patients via organizing patient support activities, as this may help elicit positive non-specific effects of acupuncture.

Currently, acupuncture's mechanism of action and hence its specific effect components, as well as its non-specific effect components, have not been completely revealed. Aside from empathy which is recognized as a non-specific effect component of almost all healthcare interventions, a recent systematic review²⁷ has summarized possible non-specific effect components of acupuncture, including: portraying professional status of the acupuncturists, adhering to holistic treatment style, explaining to patients theory supporting the effectiveness of acupuncture, modifying lifestyle in accordance to advice provided by acupuncturists, fostering a positive attitude toward treatment efficacy among patients, and patients' active engagement with the acupuncturists during consultation. These areas serve as a starting point for further investigations on how non-specific beneficial effect of acupuncture may be enhanced in clinical practice.

In this study, acupuncturists were instructed to be responsive to all patients' needs and request during consultation, but only responders expressed enhanced trust via acupuncturists' empathy and reported provision of self-care advice from acupuncturists. Patients' active engagement with the acupuncturists during consultation as a mechanism for generating non-specific effect may explain why non-responder, who may be less active during consultation, did not experience these positive effects. This implies that acupuncturists may need to take a more proactive role in generating non-specific effect, so as to facilitate positive experiences among less engaged patients.

Thirdly, in this study the use of binary outcome of "adequate relief" for classifying responders and non-responders has a limited scope as it only captures overall symptom change. This summative measure did not measure specifically other important changes in individual symptoms, health related quality of life or health utility. This implies that a non-responder may have experienced improvements in other outcomes, and we have not explored how non-specific effect influenced such change. That said, we have chosen the binary endpoint of "adequate relief" in this study as it is a common and straightforward primary outcome employed by many high quality trials in functional gastrointestinal diseases.⁷⁸ Also, an analysis of >10,000 individual patient data has shown that binary outcome has excellent construct validity when used for assessing treatment outcomes of functional gastrointestinal diseases.⁷⁹

Finally, the use of a systematic, step-by-step approach in framework analysis may reduce subjective interpretation of the results.⁸⁰ The mechanistic tendency of framework analysis could have limited creative generation of new themes from the data.⁸¹

4.4. Conclusions

Our results have provided new insights, from patient perspective, on how key non-specific effect components influence the responsiveness to acupuncture among patients with FD in a clinical trial setting. With proper implementation of these components in routine clinical practice or in research environment, positive non-specific effects contributing to the overall therapeutic effect of acupuncture may be enhanced. Future research should focus on the enhancement of model validity in trials to maximizing the generalizability of the study result. Also, how non-specific effect is influenced by mode and quantity of acupuncture information provi-

sion to patients, as well as peer support facilitated via group based treatment, will require further investigations. Quantifying the relative contribution of different non-specific effects components of acupuncture on patient outcomes could also complement our qualitative findings, and deepen our understanding on the underlying mechanism.

Author contributions

Study concept and design: RH and VC. Preparation of Pre-specified questions for the interview: RH and VC. Conducting interviews on patients: RH. Data coding and analysis: RH. and VC. Fig. preparation: RH. Tables preparation: RH. Drafting of the manuscript: RH. Revision of the manuscript, tables, Fig., and supplementary document: FFH. Giving critical intellectual comments on the manuscript: VC, JA, HC, BL, LW, and YZ.

Conflict of interests

The authors declare that they have no competing interests.

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Ethical statement

This qualitative study embedded in the randomized acupuncture trial was obtained and approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CREC Reference number: 2014.552-T).

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.imr.2021.100771](https://doi.org/10.1016/j.imr.2021.100771).

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