ORIGINAL ARTICLE

Efficacy of pancreatic enzyme replacement therapy in chronic pancreatitis: systematic review and meta-analysis

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ABSTRACT

Objective The benefits of pancreatic enzyme replacement therapy (PERT) in chronic pancreatitis (CP) are inadequately defined. We have undertaken a systematic review and meta-analysis of randomised controlled trials of PERT to determine the efficacy of PERT in exocrine pancreatic insufficiency (EPI) from CP.

Design Major databases were searched from 1966 to 2015 inclusive. The primary outcome was coefficient of fat absorption (CFA). Effects of PERT versus baseline and versus placebo, and of different doses, formulations and schedules were determined.

Results A total of 17 studies (511 patients with CP) were included and assessed qualitatively (Jadad score). Quantitative data were synthesised from 14 studies. PERT improved CFA compared with baseline (83.7±6.0 vs 63.1±15.0, p<0.00001; I²=89%) and placebo (83.2±5.5 vs 67.4±7.0, p=0.0001; I²=86%). PERT improved coefficient of nitrogen absorption, reduced faecal fat excretion, faecal nitrogen excretion, faecal weight and abdominal pain, without significant adverse events. Follow-up studies demonstrated that PERT increased serum nutritional parameters, improved GI symptoms and quality of life without significant adverse events. High-dose or enteric-coated enzymes showed a trend to greater effectiveness than low-dose or non-coated comparisons, respectively. Subgroup, sensitive and meta-regression analyses revealed that sample size, CP diagnostic criteria, study design and enzyme dose contributed to heterogeneity; data on health inequalities were lacking.

Conclusions PERT is indicated to correct EPI and malnutrition in CP and may be improved by higher doses, enteric coating, administration during food and acid suppression. Further studies are required to determine optimal regimens, the impact of health inequalities and long-term effects on nutrition.

INTRODUCTION

Chronic pancreatitis (CP) is a progressive fibro-inflammatory disorder with sustained destruction of acinar, ductal and islet cells.1 CP has an annual incidence of 4–12 per 100 000,2 increasing worldwide.3 Aetiologies include environmental toxins (prolonged, heavy alcohol exposure and cigarette smoking), hyperlipidaemia, single and/or multiple genetic mutations (PRSS1, SPINK1, CTRC, CASR, CFTR, CLDN2 and CPA1) and autoimmune disease.4–6 CP is generally progressive, with marked variation in abdominal pain and GI symptoms. These greatly impair quality of life (QoL),4 while exocrine pancreatic insufficiency (EPI) and diabetes mellitus (DM) contribute to the low median

Significance of this study
What is already known on this subject?

▸ Chronic pancreatitis (CP) is a major health problem associated with health inequalities, causing intractable abdominal pain, peripancreatic complications, exocrine pancreatic insufficiency (EPI), long-term malnutrition and type 3c diabetes mellitus.

▸ Pancreatic enzyme replacement therapy (PERT) is administered by some for EPI in CP but the benefits remain to be confirmed.

▸ No meta-analysis has been conducted previously of randomised clinical trials assessing PERT for EPI in CP, while a previous Cochrane review of PERT in CP was inconclusive.

What are the new findings?

▸ This meta-analysis shows that PERT improves the coefficients of fat and nitrogen absorption versus baseline and versus placebo, reducing faecal fat excretion, faecal nitrogen excretion, faecal weight and abdominal pain without significant adverse events. Follow-up studies have found that PERT increases serum nutritional parameters, improves GI symptoms and quality of life without significant adverse events.

▸ Although there was significant heterogeneity between trials, subgroup analyses did not alter the findings, and exclusion of trials with small sample sizes (<40) or without imaging and/or histology to establish CP significantly reduced the heterogeneity. Data on health inequalities were sparse but for those on CP aetiology attributed to alcohol excess.

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How might it impact on clinical practice in the foreseeable future?

- This systematic review and meta-analysis of 17 randomised trials of PERT for EPI in CP demonstrates the efficacy of PERT for correcting malnutrition in CP. PERT may be optimised by higher doses, enteric coating, ingestion during food and acid suppression.
- Further studies are needed to determine optimal methods to address the impact of health inequalities on PERT for EPI in CP.

Furthermore, these end points are unsuitable as primary outcome measures for studies of PERT for EPI, particularly short-term studies. For these, accurate measures that detect alterations and/or improvements in absorption are necessary. In practice, licensed enzyme replacement therapies differ greatly: granules, tablets, microspheres, minimmicrospheres or capsules with enteric coating make comparisons challenging. While the European Medicines Agency has delegated regulation of PERT to national authorities, the US Food and Drug Administration (FDA) addressed these differences in 2004 (updated in 2006), issuing requirements for new drug applications, specifying amount, stability and efficacy. To date, six enzymes have FDA approval: Creon, Pancreaze, Pertzye, Ultrase, Viokase and Zenpep, all of porcine origin.

Questions remain as to the indications for and efficacy of PERT, including methods of assessment, formulation, dose, administration and use of acid suppression. Saha et al conducted a meta-analysis of PERT for CP regardless of the presence or absence of EPI. Data for weight loss and faecal fat were combined from only two studies; the authors inferred that the evidence for any beneficial role of PERT in CP was inconclusive. Wälje et al combined trials in cystic fibrosis and CP, concluding that PERT improves but does not normalise the coefficient of fat absorption (CFA) in EPI; these two systematic reviews included a total of only three placebo-controlled trials of PERT in CP, and no quantitative data were combined to determine outcomes. Three further placebo-controlled trials of PERT in CP have since been conducted, two of which were followed by open-label extensions. We have therefore conducted a systematic review of 17 randomised controlled trials (RCTs) with meta-analysis of 14 to determine whether PERT is indicated for EPI in CP; the impact of this treatment and factors contributing to optimisation of PERT. Our study is strengthened by meta-analysis of PERT versus baseline, PERT versus placebo and PERT versus PERT to provide a more rigorous evaluation, comparing CFA, coefficient of nitrogen absorption (CNA), faecal fat excretion (FFE), faecal nitrogen excretion (FNE), faecal weight, abdominal pain and GI symptoms, bodyweight, QoL and adverse events.

**METHODS**

**Search strategy**

All studies of PERT for EPI from CP were sought in Medline (PubMed), Embase, Scopus, Science Citation Index Expanded and the Cochrane Central Register of Controlled Trials between January 1966 (the first PERT study) and December 2015. The following search terms were used in all possible combinations: Chronic adj3 pancreatitis, exocrine pancreatic insufficiency, pancrea$ insufficien$; Randomized (or randomised) controlled trial.pt., controlled clinical trial. pt, randomized.ab,placebo.ab. drug therapy.fs, randomly.ab.trial.ab.group.ab; Enzymes.tw, (enzyme$ adj1 (pancrea$ or replace$ or supplement$)).tw.(pancreati$ or pancreas or pancreaticlipase or ultras$ or cotayzm or creon or kreon or thera$ or encon or prot$ or lipase or hydro$ or exolipase or trigly$-creidase or ALTU-135).tw; English.lg. A manual reference search of reviews and conference abstracts (2006–2015) was also undertaken.

Studies meeting all the following criteria were included: (1) in English peer-reviewed journals; (2) prospective, randomised design, investigating efficacy and safety of PERT in EPI from CP in adults (age ≥18 years; including patients who had pancreatic resection for CP but not other indications); (3) reporting clinical outcomes of interest; and (4) only the most recent study of multiple overlapping patient populations from the same institution.
unless a prior study had higher quality. Abstracts, case reports, letters, expert opinions, editorials, reviews and non-RCTs were excluded.

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria were followed. Two authors (DdlI-G and WH) independently scrutinised all identified studies and reached consensus for final inclusion, with adjudication (FS) when there was disagreement.

Data extraction
Two authors (DdlI-G and WH) extracted data independently using predefined standardised forms. These captured study design, quality assessment (below), baseline characteristics, health equality indicators (ethnicity, place of residence, socioeconomic background, employment/insurance status, profession, alcohol use and cigarette smoking), diagnostic criteria for CP and EPI, exclusion criteria, trial process, details of PERT and outcomes of interest.

Outcomes of interest
CFA has been used most commonly as the primary end point to assess the efficacy of PERT on EPI due to CP and cystic fibrosis in RCTs, more informative than the presence or absence of steatorrhea.22 23 We have therefore used CFA as the primary outcome measure, calculated from fat intake (~100 g/day of dietary fat) and excretion (from 72 hours faecal collection) using the following equation:

\[
CFA(\%) = \left( \frac{\text{fat intake in g} - \text{fat excretion in g}}{\text{fat intake in g}} \right) \times 100
\]

CNA has been used to measure the effect of PERT on protein absorption in EPI, ignored in previous systematic reviews.\textsuperscript{21–23} CNA was calculated as follows:

\[
CNA(\%) = \left( \frac{\text{nitrogen intake in g} - \text{nitrogen excretion in g}}{\text{nitrogen intake in g}} \right) \times 100
\]

Secondary outcomes included CNA, FFE, FNE, faecal weight, faecal consistency (formed/normal or soft/watery), faecal frequency (stools per day), flatulence (none/mild/moderate/severe), abdominal pain (none/mild/moderate/severe) and adverse events. When available, serum nutritional markers, diarrhoea, weight loss/gain and QoL were included.

Quality assessment
Two authors (DdlI-G, WH) scored each included study using the Jadad system\textsuperscript{25} that assesses randomisation (0 or 1), double-blinding (0, 1 or 2), recording of dropouts and/or withdrawals (0 or 1) and allocation concealment (0 or 1), with a score ≥3 indicative of high quality.

Statistical analysis
Means and SDs of continuous variable were used for meta-analysis, estimated\textsuperscript{26} when medians were given. If CFA and CNA were not available, these were calculated as described. If different protocols of PERT were used in any single study, average daily lipase dose was calculated in United States Pharmacopoeia (USP) units. Meta-analyses compared PERT versus baseline, PERT versus placebo or PERT versus PERT. Forest plots were generated using Review Manager V5.3 software (Cochrane Collaboration, Oxford, UK). Continuous variables were expressed as weighted mean differences (WMD) and categorical variables as ORs with 95% CIs. A random-effects model\textsuperscript{27} was employed to ensure conservative estimates in meta-analyses. Heterogeneity was evaluated using \(\chi^2\) with p<0.1 considered significant. Statistical heterogeneity was assessed using I\(^2\) values with cut-offs of 25%, 50% and 75% to indicate low, moderate and high heterogeneity, respectively.\textsuperscript{28} Subgroup analyses examined studies of high quality; parallel, multicentre design; samples ≥40 and Western populations. Sensitivity analyses were conducted by diagnostic criteria and inclusion of pancreatic surgery.

Meta-regression analyses assessed influence of age, gender, study design, study quality, lipase dose and publication year on summary estimates using Stata SE V13 Software (StataCorp, Texas, USA); p<0.05 was considered significant. Publication bias was assessed using funnel plots,\textsuperscript{29} and p values generated from both CFA and FFE as per Beggg and Mazumdar\textsuperscript{30} and Egger et al.,\textsuperscript{31} p<0.10 was considered significant.

Patient and public involvement
The research design, methods, results and their interpretation were reviewed by the NIHR Liverpool Pancreas Biomedical Research Unit Patient Advisory Group, and modifications made accordingly. The group is comprised of patients with a history of acute pancreatitis, CP or pancreatic cancer, or their carers, or interested members of the public.

RESULTS
Design and quality assessment of included studies
The PRISMA flow diagram is shown in figure 1; 17 studies\textsuperscript{32–48} were included. Study design and quality assessment are shown in table 1. There were four\textsuperscript{32–34,40,45} conducted in the USA, nine\textsuperscript{34,39,41,43–46} in Europe, two\textsuperscript{47,48} in the USA and Europe, one\textsuperscript{42} in South Africa and one\textsuperscript{48} in India. Twelve\textsuperscript{32–35,38,39,41–43,47–49} had cross-over designs (two\textsuperscript{42} multicentre); five\textsuperscript{38,42,45,46,48} had parallel designs (three\textsuperscript{45,46} multicentre). Five\textsuperscript{41,43,46–48} reported sample size calculations, four\textsuperscript{41} using change of CFA values and one\textsuperscript{43} cumulative 13CO\(_2\) recovery rate. Detailed Jadad scoring is shown in online supplementary.
table S1. All seven high-quality studies33 35 38 41–48 were double-blinded.

Baseline parameters of patients with CP

These are shown in online supplementary table S2; 511 patients with CP were enrolled and 477 analysed; median age was 50 years. Gender was reported in most studies (poled 76.4% males). Ethnicity was reported in only four.45–48 None reported residence data, smoking, socioeconomic status or profession. Five41 42 46–48 reported body mass index. Nine12 33 35 36 39 40 42 44 48 included data on coexisting DM (pooled frequency 49.5%). Patients in seven studies32 33 39 did not report a run-in phase. The trial. Three studies41 42 48 reported a 14-day run-in with the last seven days before randomisation treated by PERT. The remaining three studies32 33 39 did not report a run-in phase. During treatment, PERT or placebo was used with or without a washout in between switching treatments. Daily fat intake was recorded in the majority (normally 100 g/day), but not in three.36 37 44 Only three37 46 47 reported use of a faecal dye. The equilibration time was normally 2–5 days before a 3-day period of faecal fat collection. Adverse events were reported in six,36 41 45–48 with an incidence of 11.4–42.7%.

RCT study duration ranged from several days to 2 months; none assessed long-term effects of PERT, although two open-label extension studies examined the nutritional impact of PERT over 6 months19 and 12 months.50

Composition and administration schedule of PERT

Details of PERT composition and administration schedules are shown in online supplementary table S3. Converted pancreatic lipase doses in USP units are shown in figure 2. The source of pancreatic enzymes and conversion factors is shown in online supplementary table S4. PERT formulations were granules, micrtablets, microspheres and minimicrospheres with or without enteric coating. Four studies12–14 36–38 included non-coated and enteric-coated enzymes. Two studies46 47 used delayed release enteric-coated minimicrospheres (Creon 12000) or microspheres (Zenpep).

Details of trial process

The trial process and adverse events are shown in table 2. RCTs of PERT typically had a run-in phase to scrutinise and stabilise eligible participants before treatment initiation. During run-in or washout, PERT was stopped. Six studies34–37 43 44 reported a 3–15-day no-treatment run-in, while five38 40 45–47 had a 5–14-day period for placebo administration before commencing the trial. Three studies41 42 48 reported a 14-day run-in with the last seven days before randomisation treated by PERT. The remaining three studies32 33 39 did not report a run-in phase. During treatment, PERT or placebo was used with or without a washout in between switching treatments. Daily fat intake was recorded in the majority (normally 100 g/day), but not in three.36 37 44 Only three37 46 47 reported use of a faecal dye. The equilibration time was normally 2–5 days before a 3-day period of faecal fat collection. Adverse events were reported in six,36 41 45–48 with an incidence of 11.4–42.7%.

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Delhaye’s study19 found no significant differences in the efficacy of Pancrease HL and Creon 3 (both enteric-coated microspheres). Halm’s study35 showed the primary outcome CFA and adverse events to be similar for Creon 10000 microspheres and minimicrospheres with or without enteric coating. Four studies12–14 36–38 included non-coated and enteric-coated enzymes. Two studies46 47 used delayed release enteric-coated minimicrospheres (Creon 12000) or microspheres (Zenpep).
<table>
<thead>
<tr>
<th>Study</th>
<th>Criteria for chronic pancreatitis</th>
<th>Criteria for exocrine pancreatic insufficiency before randomisation</th>
<th>Run-in (washout) phase</th>
<th>Treatment phase</th>
<th>Fat in diet/day (g)</th>
<th>Faecal dye</th>
<th>Controlled timing of faecal fat collection</th>
<th>Adverse events</th>
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</thead>
<tbody>
<tr>
<td>Graham^32</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>6 days for each of the four PERT preparations</td>
<td>100</td>
<td>3-day equilibration followed by 3-day collection</td>
<td>NR</td>
</tr>
<tr>
<td>Dutta et al^33</td>
<td>Radiological evidence of pancreatic calcifications or multiple strictures in MPD, or histological evidence</td>
<td>Normal d-xylene absorption; marked abnormal secretin test; FFE &gt;7 g/day on a 100 g/day fat intake</td>
<td>NR</td>
<td>NR</td>
<td>3 days for each of the two PERT preparations</td>
<td>100</td>
<td>3-day equilibration followed by 3-day collection</td>
<td>NR</td>
</tr>
<tr>
<td>Lankish et al^34</td>
<td>Typical disease history and/or histology</td>
<td>Abnormal secretin-pancreozymin test; FFE &gt;15 g/day</td>
<td>3 days</td>
<td>5 days for each of the three PERT preparations</td>
<td>100</td>
<td>2-day equilibration followed by 3-day collection</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Halgreen et al^35</td>
<td>Imaging indicative of pancreatic calcification, previous acute attacks and/or typical abnormalities by ERCP</td>
<td>Meal stimulated duodenal lipase &lt;50 kU/L and FFE &gt;8 g/day</td>
<td>14 days</td>
<td>14 days for PERT or placebo then vice versa</td>
<td>100</td>
<td>2-day equilibration followed by 3-day collection</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Gouerou et al^36</td>
<td>Imaging indicative of pancreatic calcification, ERCP abnormalities or other histological signs</td>
<td>FFE &gt;8 g/day</td>
<td>10 days</td>
<td>21 days each for either two PERT preparations then vice versa</td>
<td>NR</td>
<td>NR</td>
<td>3 days before treatment and 3 days at the end of each treatment period</td>
<td>PERT 1: 11.4%; PERT 2: 11.4%</td>
</tr>
<tr>
<td>Jørgensen et al^37</td>
<td>Pancreatic calcifications on US, ERCP, CT and/or anatomy abnormalities in laparotomy</td>
<td>Meal stimulated duodenal enzyme activity below 10% and FFE 15 g/day on free diet</td>
<td>7 days</td>
<td>7 days for each of the two PERT preparations</td>
<td>NR</td>
<td>Yes, brilliant blue</td>
<td>3 days before treatment and after 7 days of each treatment</td>
<td>NR</td>
</tr>
<tr>
<td>Paris^38</td>
<td>Radiology of preoperative confirmation</td>
<td>FFE &gt;10 g/day</td>
<td>7–9 days placebo followed by 5 days</td>
<td>8-day PERT or placebo</td>
<td>&gt;100</td>
<td>NR</td>
<td>4-day equilibration followed by 3-day collection</td>
<td>PERT: 10.3%; placebo: 9.1%</td>
</tr>
<tr>
<td>Delhaye et al^39</td>
<td>Pancreatic calcifications, typical abnormalities in ERCP, or histology</td>
<td>FFE &gt;10 g/day</td>
<td>NR</td>
<td>14 days for each of the four PERT preparations followed by 5 days of standard diet period in between</td>
<td>&gt;100</td>
<td>NR</td>
<td>14-day equilibration followed by 3-day collection</td>
<td>NR</td>
</tr>
<tr>
<td>Opekun Jr et al^40</td>
<td>Documented symptomatic steatorrhoea</td>
<td>Documented symptomatic steatorrhoea</td>
<td>6-day placebo</td>
<td>6 days for each of the three PERT preparations and a placebo with 2-day washout period in between</td>
<td>100</td>
<td>NR</td>
<td>3-day equilibration followed by 3-day collection</td>
<td>NR</td>
</tr>
<tr>
<td>Halm et al^41</td>
<td>US, CT, ERCP or X-ray indicative of pancreatic calcification and &lt;6 acute attacks</td>
<td>FFE &gt;7.5 g/day</td>
<td>7-day placebo followed by 7-day PERT MS</td>
<td>14 days of each two PERT MS and MMS with a 7-day washout period in between</td>
<td>70–80</td>
<td>NR</td>
<td>4-day equilibration followed by 3-day collection, 11-day equilibration followed by 3-day collection in PERT period</td>
<td>PERT MS: 21.7%; PERT MMS: 17.4%</td>
</tr>
<tr>
<td>O’Keefe et al^42</td>
<td>Typical signs of chronic pancreatitis in CT, US, ERCP or pancreatic calcification in X-ray</td>
<td>FFE &gt;10 g/day</td>
<td>7-day placebo followed by 7-day PERT</td>
<td>14-day PERT or placebo</td>
<td>–100</td>
<td>NR</td>
<td>4-day equilibration followed by 3-day collection in placebo period, 11-day equilibration followed by 3-day collection in PERT period</td>
<td>NR</td>
</tr>
<tr>
<td>Dominguez-Muñoz et al^43</td>
<td>Severe chronic pancreatitis diagnosed by MRI, CT and/or EUS (Cambridge and Wiersema criteria)</td>
<td>FFE &gt;7 g/day</td>
<td>&gt;5 days</td>
<td>7 days for each of the three PERT preparations (consecutive)</td>
<td>92</td>
<td>NR</td>
<td>5-day equilibration followed by 3-day collection</td>
<td>NR</td>
</tr>
<tr>
<td>Vecht et al^44</td>
<td>Clinical history, alterations of pancreatic morphology in CT, ERCP (Cambridge score)</td>
<td>FFE &gt;10 g/day</td>
<td>15 days</td>
<td>15 days each for either high or low dose of PERT preparation then vice versa</td>
<td>NR</td>
<td>NR</td>
<td>3-day collection</td>
<td>NR</td>
</tr>
<tr>
<td>Safdi et al^45</td>
<td>Documented chronic pancreatitis</td>
<td>CFA &lt;80% and/or FFE &gt;10 g/day in run-in phase; study compliance</td>
<td>14-day placebo</td>
<td>14-day PERT or placebo</td>
<td>&gt;100</td>
<td>NR</td>
<td>11-day equilibration followed by 3-day collection</td>
<td>PERT: 23.1%; placebo: 35.7%</td>
</tr>
</tbody>
</table>

Continued
units/day) Zenpep without acid inhibition both significantly improved CFA, CNA, bodyweight and body mass index. Subgroup analysis, however, revealed that a higher dose of PERT may be needed for more severe EPI. Domínguez-Muñoz’s study suggested that PERT administration during or after meals may be more appropriate than before meals. In all other studies, PERT was taken before or with meals or snacks at various different doses. The use of proton pump or H2 inhibitors was reported or allowed in five with only one comparing PERT versus PERT without omeprazole; in this last study, omeprazole improved fat digestion but compromised protein digestion.

Meta-analysis results
In total, 14 of 17 included studies on EPI with PERT (WMD: 0.61 – 0.03 to 1.24; P = 0.06). Thirteen studies (86%) found that PERT significantly reduced CFA compared to placebo (P < 0.001). PERT was more effective in reducing CFA than placebo (P < 0.001). Nine studies (53%) found that PERT significantly reduced CFA versus baseline (P < 0.001). PERT was more effective in reducing CFA compared to baseline (P < 0.001). PERT was more effective in reducing CFA than placebo (P < 0.001). PERT was more effective in reducing CFA compared to baseline (P < 0.001). PERT was more effective in reducing CFA compared to placebo (P < 0.001). PERT was more effective in reducing CFA compared to baseline (P < 0.001). PERT was more effective in reducing CFA compared to placebo (P < 0.001). PERT was more effective in reducing CFA compared to baseline (P < 0.001). PERT was more effective in reducing CFA compared to placebo (P < 0.001).

The clinical outcomes of PERT versus placebo are presented in figure 3 and summarized in table 3. Eleven studies reported CFA versus baseline (WMD: 0.30; 95% CI: 0.03, 0.45) and baseline (WMD: 0.18; 95% CI: 0.12, 0.28) and placebo (WMD: 0.12; 95% CI: 0.05, 0.21). PERT increased CFA versus baseline (WMD: 0.22; 95% CI: 0.07, 0.38) and placebo (WMD: 0.12; 95% CI: 0.05, 0.21). PERT increased CFA versus baseline (WMD: 0.22; 95% CI: 0.07, 0.38) and placebo (WMD: 0.12; 95% CI: 0.05, 0.21). PERT increased CFA versus baseline (WMD: 0.22; 95% CI: 0.07, 0.38) and placebo (WMD: 0.12; 95% CI: 0.05, 0.21). PERT increased CFA versus baseline (WMD: 0.22; 95% CI: 0.07, 0.38) and placebo (WMD: 0.12; 95% CI: 0.05, 0.21). PERT increased CFA versus baseline (WMD: 0.22; 95% CI: 0.07, 0.38) and placebo (WMD: 0.12; 95% CI: 0.05, 0.21). PERT increased CFA versus baseline (WMD: 0.22; 95% CI: 0.07, 0.38) and placebo (WMD: 0.12; 95% CI: 0.05, 0.21). PERT increased CFA versus baseline (WMD: 0.22; 95% CI: 0.07, 0.38) and placebo (WMD: 0.12; 95% CI: 0.05, 0.21). PERT increased CFA versus baseline (WMD: 0.22; 95% CI: 0.07, 0.38) and placebo (WMD: 0.12; 95% CI: 0.05, 0.21). PERT increased CFA versus baseline (WMD: 0.22; 95% CI: 0.07, 0.38) and placebo (WMD: 0.12; 95% CI: 0.05, 0.21). PERT increased CFA versus baseline (WMD: 0.22; 95% CI: 0.07, 0.38) and placebo (WMD: 0.12; 95% CI: 0.05, 0.21). PERT increased CFA versus baseline (WMD: 0.22; 95% CI: 0.07, 0.38) and placebo (WMD: 0.12; 95% CI: 0.05, 0.21). PERT increased CFA versus baseline (WMD: 0.22; 95% CI: 0.07, 0.38) and placebo (WMD: 0.12; 95% CI: 0.05, 0.21). PERT increased CFA versus baseline (WMD: 0.22; 95% CI: 0.07, 0.38) and placebo (WMD: 0.12; 95% CI: 0.05, 0.21). PERT increased CFA versus baseline (WMD: 0.22; 95% CI: 0.07, 0.38) and placebo (WMD: 0.12; 95% CI: 0.05, 0.21).
Figure 3  The pooled clinical outcomes of pancreatic enzyme replacement therapy (PERT) versus baseline. (A) coefficient of fat absorption (CFA), (B) coefficient of nitrogen absorption (CNA), (C) faecal fat excretion (FFE), (D) faecal nitrogen excretion (FNE) and (E) faecal weight.
with enteric-coated microspheres, although not statistically significant (85.7±4.6 vs 75.4±10.0; WMD: 0.70, 95% CI: 0.27 to 1.67; p=0.16). Similar findings were made from four studies reporting FFE with small sample sizes (n=18–55) and high heterogeneity.

### Subgroup analysis

Subgroup analyses of PERT versus baseline for studies of high-quality, parallel multicentre, sample size ≥40 and in Western populations did not change primary meta-analysis results or statistical heterogeneity for CFA and FFE (table 4). Subgroup analyses of PERT versus placebo were similar, but heterogeneity was significantly reduced when sample size ≥40 for CFA (I²=66% to 63%) and FFE (I²=68% to 66%).

### Sensitivity analysis

Sensitivity analyses were performed as described in online supplementary table S5. For PERT versus baseline, the results and heterogeneity of CFA and FFE were not affected by diagnostic criteria for CP or EPI or by pancreatic surgery or by only including studies with a proper run-in phase. Heterogeneity in PERT versus placebo disappeared however for both CFA (I²=0%; p=0.70) and FFE (I²=0%; p=0.92) when only including CP defined by imaging and/or histology.
Figure 4  The pooled clinical outcomes of pancreatic enzyme replacement therapy (PERT) versus placebo. (A) coefficient of fat absorption (CFA), (B) coefficient of nitrogen absorption (CNA), (C) faecal fat excretion (FFE), (D) faecal nitrogen excretion (FNE), (E) faecal weight and (F) adverse events.
Meta-regression analysis
Covariates of study design (p=0.04) and daily lipase dose (p=0.07) appeared to contribute to heterogeneity for FFE (see online supplementary table S6); age, gender, study quality and year of publication did not; limited data prevented assessment of alcohol and DM.

Publication bias
There was no significant evidence of publication bias for either CFA (see online supplementary figure S1) or FFE (see online supplementary figure S2) in PERT versus baseline, PERT versus placebo, high dose versus low dose and enteric-coated versus non-coated (Begg and Egger: p>0.10 for all comparisons).

Extension studies
A 6-month, open-label trial49 (Creon 12000) extension of Whitcomb’s study46 found PERT well tolerated, significantly improving serum nutritional parameters (retinol-binding protein, prealbumin, albumin and cholesterol) and weight, reducing faecal frequency, although no meaningful changes of QoL scores were observed. A 51-week, open-label extension trial50 from Thorat’s study showed that Creon 40000 significantly improved laboratory nutritional parameters, fat and protein absorption, GI symptoms and QoL, with a favourable safety and tolerability profile.

DISCUSSION
We found PERT to improve fat and protein absorption significantly in CP, demonstrated by marked, consistent increases in CFA and CNA compared with baseline or placebo. Significant reductions in FFE, FNE, faecal weight and improvements in GI symptoms were also observed across RCTs, unchanged by subgroup, sensitivity and meta-regression analyses. Unlike in the previous Cochrane review with meta-analysis of only two studies,21 our meta-analysis of 14 RCTs demonstrates that PERT is clearly indicated in CP for EPI. Even though long-term effects on complications and mortality could not be determined, these
findings are similar to PERT for EPI in cystic fibrosis,\(^\text{22, 23}\) which, if extrapolated, suggest long-term benefit. Although no RCT was conducted over a period longer than 2 months, two open-label extensions of up to 1 year demonstrated significant improvements in serum nutritional parameters, weight, GI symptoms and QoL. Despite PERT not wholly normalising fat absorption, driving the search for better enzymes and/or correction of other factors,\(^\text{6}\) the safety profile of PERT was comparable to placebo, also favourable in the extension studies.

Healthy nutrient digestion and absorption requires complex coordination of mechanical and enzymatic breakdown of food, a finely tuned process depending on integration of multiple upper GI functions including regulated, plentiful pancreatic exocrine and biliary secretion.\(^\text{9}\) Breakdown of fat relies on pancreatic lipase, which is highly susceptible to gastric acid; normally pancreatic bicarbonate secretion ensures intra-duodenal pH of 5–6 for optimal enzymatic activity, also preventing bile acid precipitation. One study found that endogenous lipase activity has to fall to <10% of normal before steatorrhoea occurs\(^\text{15}\) and thus PERT should deliver ≥10% of normal lipase activity. The amount of postprandial lipase secreted in a healthy adult is estimated at between 9000 and 18 000 USP units/min for up to 4 hours.\(^\text{9}\) Therefore, delivery of at least 100 000 USP units per meal (up to 400 000 USP units/120 000 international units in severe EPI) is required to correct EPI in adult CP; although we found a trend for higher doses to increase CFA, this increase was not statistically significant and did not fully correct malabsorption. Gastric acid inhibition can further enhance the efficacy of PERT;\(^\text{44, 51, 52}\) we found equal efficacy of PERT at higher doses alone compared with lower doses with gastric acid suppression therapy, and an RCT not varying PERT between groups found acid suppression therapy to significantly improve fat absorption.\(^\text{52}\) Further improvement may occur if PERT is given during meals,\(^\text{63}\) corresponding with normal peak enzyme secretion some 30 min after food, followed by an elevated plateau.\(^\text{9}\) Future RCTs are required for definitive conclusions on PERT optimisation.

EPI is frequent but variable in CP and typically progressive over a number of years,\(^\text{1, 3–5, 8}\) contributing to long-term complications from malnutrition. Quantification of CFA and/or FFE is rarely undertaken routinely and clinical assessments of EPI are inexact; EPI may be inferred from patient and imaging characteristics, deficiencies in fat-soluble vitamins and osteoporosis, or identified by endoscopic pancreatic function testing (normal peak pancreatic bicarbonate secretion >80 mEq/L).\(^\text{2}\) Lipid-soluble vitamins, retinol-binding protein, albumin and prealbumin may be useful to monitor responses to PERT.\(^\text{49, 50}\) Nevertheless, once the diagnosis of CP is established and since some degree of EPI is likely,\(^\text{3, 8, 16–19}\) PERT is the treatment of choice to reduce and/or minimise long-term malnutrition, unless pancreatic secretion is demonstrated to be normal. Support for this comes from a prospective, non-randomised, multicentre 1-year cohort study of 206 patients with EPI from CP already on PERT and 88 with newly diagnosed EPI from CP newly prescribed PERT.\(^\text{51}\) EPI was identified by malabsorption/diarrhoea/steatorrhoea, weight loss, meteorism, dyspepsia, recurrent pain, nausea and vomiting. PERT was associated with significant reductions in recurrent abdominal pain, GI symptoms and GI

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### Table 4  Results of subgroup analyses

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Patients, n</th>
<th>Patients, n</th>
<th>Effect estimate</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PERT</td>
<td>Baseline or placebo</td>
<td>WMD/OR (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td><strong>PERT vs baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CFA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-quality studies</td>
<td>5 172</td>
<td>174</td>
<td>1.78 (0.85 to 2.70)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Parallel designed</td>
<td>5 115</td>
<td>115</td>
<td>2.47 (1.42 to 3.52)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Multicentre studies</td>
<td>4 140</td>
<td>140</td>
<td>2.13 (0.84 to 3.43)</td>
<td>0.001</td>
</tr>
<tr>
<td>Sample size ≥40</td>
<td>4 160</td>
<td>160</td>
<td>1.26 (0.51 to 2.00)</td>
<td>0.001</td>
</tr>
<tr>
<td>Western population</td>
<td>10 196</td>
<td>197</td>
<td>1.17 (0.94 to 1.40)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td><strong>FFE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-quality studies</td>
<td>5 172</td>
<td>174</td>
<td>−1.44 (−2.18 to −0.71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Parallel designed</td>
<td>5 115</td>
<td>117</td>
<td>−1.66 (−2.19 to −1.13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multicentre studies</td>
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<td>−1.67 (−2.67 to −0.66)</td>
<td>0.001</td>
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<tr>
<td>Sample size ≥40</td>
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<td>162</td>
<td>−0.60 (−1.61 to −0.50)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Western population</td>
<td>12 246</td>
<td>247</td>
<td>−1.70 (−2.29 to −1.12)</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

CFA, coefficient of fat absorption; FFE, faecal fat excretion; PERT, pancreatic enzyme replacement therapy; WMD, weighted mean difference.
QOL index (all \( p < 0.001 \)) in both cohorts, although uncertainty remains as to how PERT reduces intestinal and/or pancreatic pain. Despite use of the more conservative random-effects model, we found significant heterogeneity between studies. Subgroup analyses, however, did not alter estimates of the effect of PERT versus baseline or placebo on CFA and FFE, nor estimates of heterogeneity, although restriction of analysis to larger studies reduced heterogeneity. Sensitivity analyses did not alter estimates for CFA and FFE, but heterogeneity was abolished for FFE in PERT versus placebo when CP was diagnosed by imaging and/or histology criteria. The heterogeneity identified highlights the need for greater international consensus on the definition and diagnosis of CP. Access to medical expertise, compliance, diet and lifestyle is heavily influenced by health inequalities. Proxy indicators, notably alcohol usage and cigarette smoking, are themselves independently associated with progression of CP and nutrient deprivation. In our study, 76.4\% of patients were male and 89.1\% of patients had alcohol-associated CP, but none of the RCTs reported measures of smoking, residence, socioeconomic or employment status, diet or comorbidity. As genetic factors and smoking and smoking have become increasingly recognised in CP progression, health inequalities should be addressed in future studies of PERT to increase the applicability of findings to all patients with CP.

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Contributors DdlI-G and WH are co-first authors. RS and JED-M conceived, designed and supervised the study, and obtained funding. DdlI-G, WH, PS, IB-R, RS, RP, RM, QMN acquired, analysed and interpreted the data. DdlI-G, WH and RS wrote the paper; JED-M and NIHR BRU PAG undertook critical revision of the manuscript for important intellectual content.

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Data sharing statement Upon publication raw data from individual studies will be made available by the corresponding author to interested researchers requesting data for bona fide scientific purposes.

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