Essential phospholipids (EPLs) – efficacy across the spectrum of NAFLD origins

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Disclosures

- Prof. Sas certifies that there is no conflict of interests with any financial organization regarding the material discussed in these slides

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Current medical treatments of NAFLD with comorbidities are experimental

Treatments for comorbidities of NAFLD

Standard treatment
Metformin
PPAR-γ agonists
PPAR-α agonists, statins and ezetimibe
Vitamin E
DPP-4 inhibitors
GLP-1 agonists

Traditional and herbal
N-Acetyl Cysteine
R-alpha lipoic acid
Choline Bitartrate
Artichoke extract
Dandelion root
Turmeric (curcumin)
Liv. 52 (Himalaya plants)
Gansu (Ganoderma)

Hepatoprotectives
Milk thistle extract (Silymarin)
EPL
Ursodeoxycholic acid
Vitamin E (antioxidant)
Glutathione
SAMe

Investigational treatment
Obeticholic Acid
Elafibrinor
Selonsertib
Emricasan
Cenicriviroc
Aramchol

- There is inconsistent evidence for the standard medications used for comorbid conditions of NAFLD
- Traditional agents lack supportive research
- Hepatoprotective agents remain an important, reliable part of the treatment protocol

DPP-4, dipeptidyl peptidase-4; EPL, essential phospholipids; GLP-1, glucagon-like peptide-1; NAFLD, non-alcoholic fatty liver disease; PPAR, peroxisome proliferator-activated receptor; SAMe, S-adenosylmethionine

Dajani A, et al. Saudi J Gastroenterol 2016;22:91–105

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EPLs have cellular and sub-cellular functions, and could be used to treat liver diseases of various origins

Functions of EPLs

- Activation of phospholipid-dependent enzymes
- Metabolic effects:
  - Accelerate synthesis of lipoproteins and convert neutral fats and cholesterol into easily metabolised forms
  - Activate synthesis of RNA and normalise protein metabolism
  - Increase synthesis of glycogen in the liver
- Improve detoxification function of the liver
- Decrease fatty infiltration of hepatocytes
- Inhibit or correct fibrogenic processes
- Influence apoptosis
- Anti-inflammatory and anti-oxidant properties

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease
Gundermann KJ, et al. Pharmacol Rep 2011;63:643–59

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Indications for EPL treatment

- Autoimmune disease of the liver
- Cirrhosis of the liver
- Alcoholic steatohepatitis
- NAFLD
- Drug-induced liver injury
- Viral hepatitis

EPLs are indicated in a variety of liver diseases, including NAFLD

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease
Gundermann KJ, et al. Pharmacol Rep 2011;63:643–59

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How familiar are you with the data supporting the use of EPL therapy across the spectrum of fatty liver disease?

1. Very familiar
2. Somewhat familiar
3. Not very familiar
4. I am not aware of any data on the use of EPL

EPL, essential phospholipid

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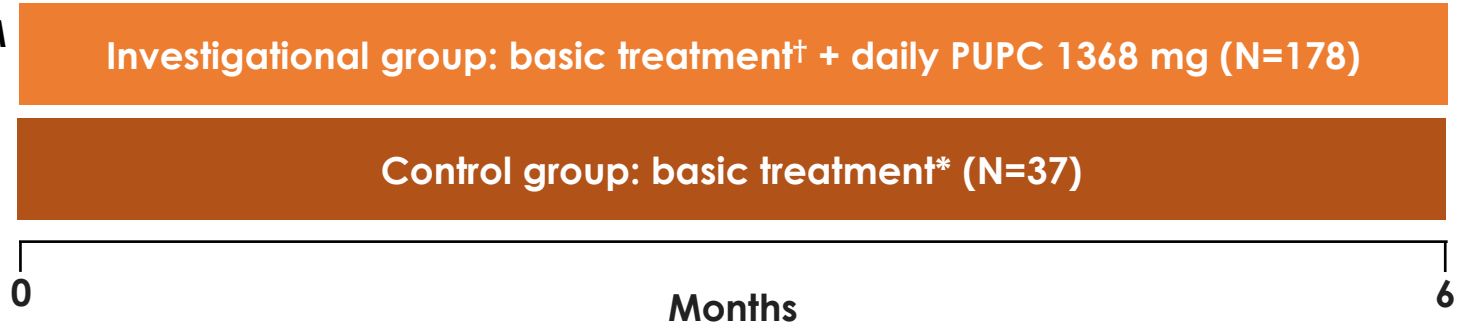
Effect of EPLs on liver function in patients with T2DM and NASH: study design

Randomised, prospective, single-blind clinical trial investigating the effect of PUPC* in patients with T2DM and NASH

N=215 patients with T2DM of an uncomplicated course which was adequately controlled by diet and treatment with metformin



Primary endpoints: markers of liver function (ALT, AST and γ-GT) and ultrasound results

*Essentiale® forte N, produced by A Nattermann and Cie GmbH; †Basic treatment included a dietary and physical regimen and treatment with metformin 1000 mg/day; ‡This study had a 7-year follow-up not shown here. PUPC refers to phosphatidylcholine molecules carrying essential fatty acids.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; EPL, essential phospholipids; γ-GT, gamma glutamyl transferase; NASH, non-alcoholic steatohepatitis; PUPC, polyunsaturated phosphatidylcholine; T2DM, type 2 diabetes mellitus
Sas E, et al. J Hepatol 2013;58:S549

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Effect of EPLs on liver function in patients with T2DM and NASH

Changes in liver enzyme levels from baseline to 6 months following EPL treatment

- All **liver enzymes** were **significantly reduced** following EPL treatment compared with standard of care
- Significant reductions in HbA1c, leading to **improved glycaemic control**, were observed in **86%** of patients receiving EPLs

	Study endpoints	EPL (N=178)
ALT	Baseline 6 months p value	56.5 ± 28.6 IU/L 35.2 ± 18.4 IU/L p=0.02
AST	Baseline 6 months p value	39.0 ± 9.0 IU/L 26.5 ± 7.2 IU/L p=0.04
γ-GT	Baseline 6 months p value	38.2 ± 11.4 IU/L 27.5 ± 8.6 IU/L p=0.03

Data are mean ± SD
ALT, alanine aminotransferase; AST, aspartate aminotransferase; EPL, essential phospholipid; HbA1c, glycated haemoglobin; NASH, non-alcoholic steatohepatitis; SD, standard deviation; T2DM, type 2 diabetes mellitus; γ-GT, gamma glutamyl transferase
Sas E, et al. J Hepatol 2013;58:S549

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Effect of EPLs on liver function in patients with T2DM and NASH

Changes in hepatic echo-texture and signs of fatty liver following 6 months of EPL treatment

- **Hepatic echo-texture** was significantly improved with EPLs versus standard of care
- Sonographic signs of **fatty liver** significantly decreased with EPLs versus standard of care
- The development of **hepatic fibrosis** was significantly slowed down with EPLs compared with control (p=0.03)

	Study	EPL (N=178)
Ultrasound studies (hepatic echo-texture)	Improvement	101/152 (66.4%)*
	No change	7/152 (4.6%)
Sonographic signs of fatty liver	Decrease	93/114 (81.6%)**

*p=0.02; **p<0.05. Data shown as n (%)
EPL, essential phospholipid; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus
Sas E, et al. J Hepatol 2013;58:S549

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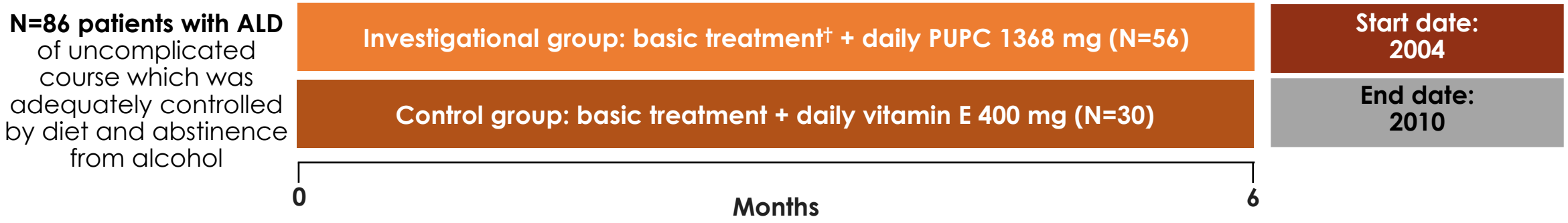
Effect of EPLs on liver function in patients with ALD: study design

Randomised, prospective, single-blind clinical trial investigating the effect of PUPC* in patients with ALD



Primary endpoints: liver biopsy, markers of liver function (ALT, AST and γ-GT) and ultrasound results

*Essentiale® forte N produced by A. Nattermann & Cie. GmbH; †Basic treatment included a dietary and physical regimen and abstinence from alcohol. PUPC refers to phosphatidylcholine molecules carrying essential fatty acids.
ALD, alcoholic liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EPL, essential phospholipid; PUPC, polyunsaturated phosphatidylcholine; γ-GT, gamma glutamyl transferase
Sas E, et al. J Hepatol 2011;54:S506

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Effect of EPL treatment on liver function in patients with ALD

Changes in liver enzyme levels from baseline to 6 months following EPL treatment

- Levels of all **liver enzymes** were significantly reduced after 6 months of treatment with EPLs compared with the control group
- There were reductions in **glucose** and **insulin levels** and insulin resistance index scores in patients treated with EPLs

	Study endpoints	EPL (N=56)
ALT	Baseline 6 months p value	74.5 ± 8.6 IU/L 31.2 ± 8.4 IU/L p<0.04
AST	Baseline 6 months p value	79.0 ± 11.2 IU/L 31.5 ± 6.5 IU/L p<0.02
γ-GT	Baseline 6 months p value	88.2 ± 12.4 IU/L 47.5 ± 5.3 IU/L p<0.03

Data are mean ± SD
ALD, alcoholic liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EPL, essential phospholipid; γ-GT, gamma glutamyl transferase; SD, standard deviation
Sas E, et al. J Hepatol 2011;54:S506

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Effect of EPL treatment on liver function in patients with ALD

Changes in hepatic echo-texture following 6 months of EPL treatment

- Ultrasound images demonstrated improvement in **hepatic echo-texture** in **87.5%** of patients after treatment with EPLs
- Liver biopsy and FibroMAX™ test showed that the progression of **hepatic fibrosis** was significantly slower in the group receiving EPLs compared with the control group

	Study	EPL (N=56)
Ultrasound studies (hepatic echo-texture)	Improvement	49/56 (87.5%)
	No change	7/56 (12.5%)

Data shown as n (%)
ALD, alcoholic liver disease; EPL, essential phospholipid
Sas E, et al. J Hepatol 2011;54:S506

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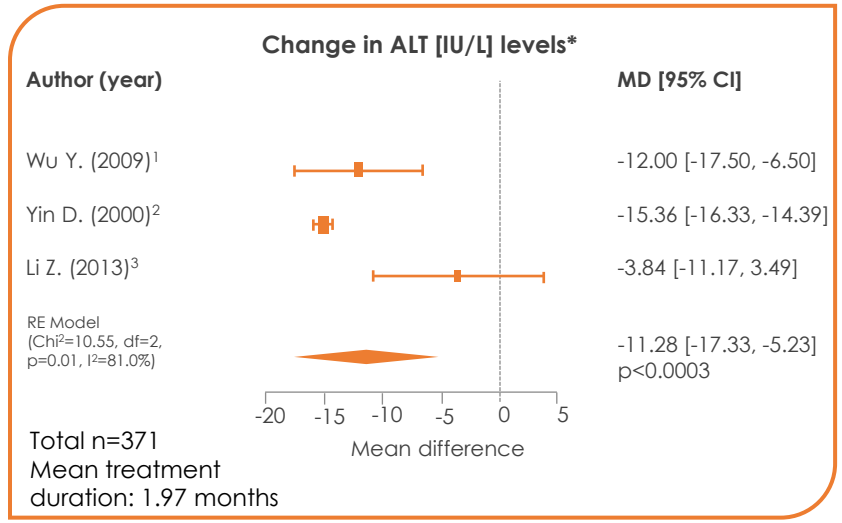
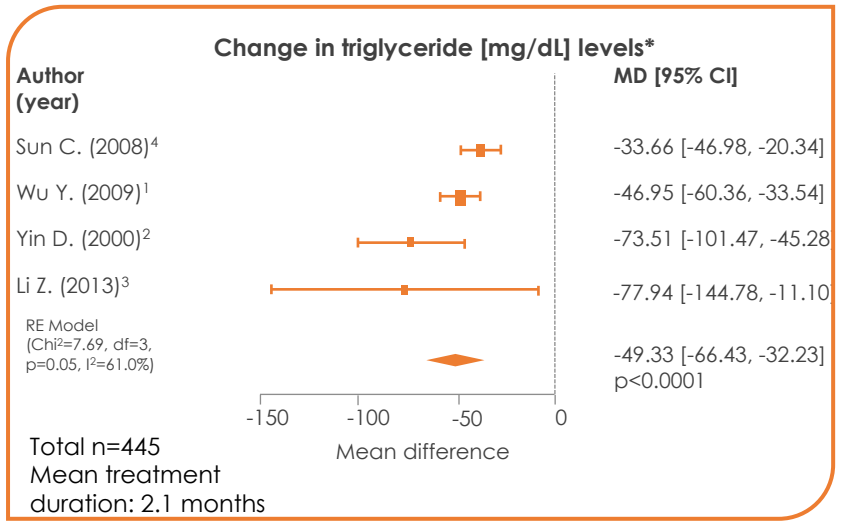
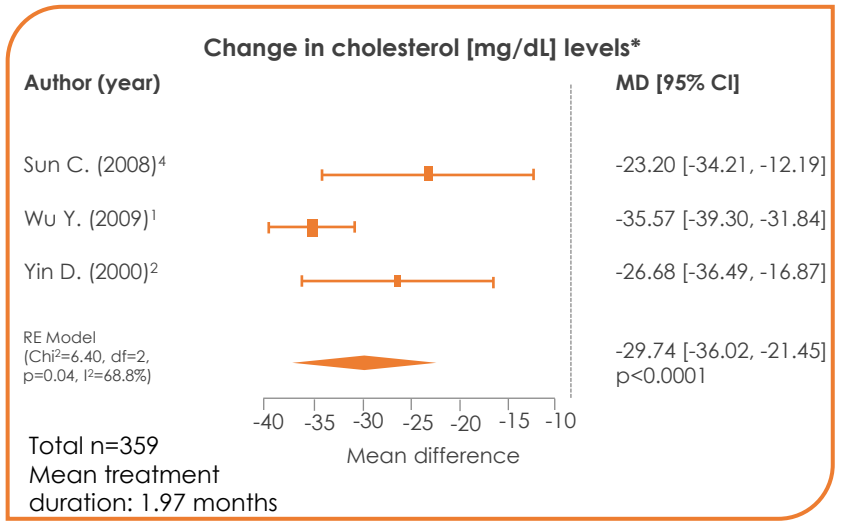
EPLs for NAFLD associated with metabolic syndrome: a systematic review and network meta-analysis (1/3)

Results of a direct meta-analysis of RCTs comparing the effect of treatment with EPLs + AD vs AD alone[5]







A significantly greater reduction in **ALT** levels was achieved with EPL + AD therapy compared with AD therapy alone

A significantly greater reduction in **triglyceride** levels was achieved with EPL + AD compared with AD therapy alone

A significantly greater reduction in total **cholesterol** levels was achieved with EPL + AD compared with AD therapy alone

*<0 favours EPL >0 favours control
AD, anti-diabetic treatment; ALT, alanine aminotransferase; CI, confidence interval; df, degrees of freedom; EPL, essential phospholipid; MD, mean difference; RCT, randomised controlled trial; RE, random effects

1. Wu Y. J TCM Univ. Hunan 2009;29:41–2; 2. Yin D, et al. Med JQ illu 2000;15:277–8; 3. Li Z. J Tradit Chinese Med 2013;31:10–1; 4. Sun C, et al. Clin Focus 2008;23:1272–3; 5. Dajani A, et al. World J Clin Cases 2020;8(21):5235–49

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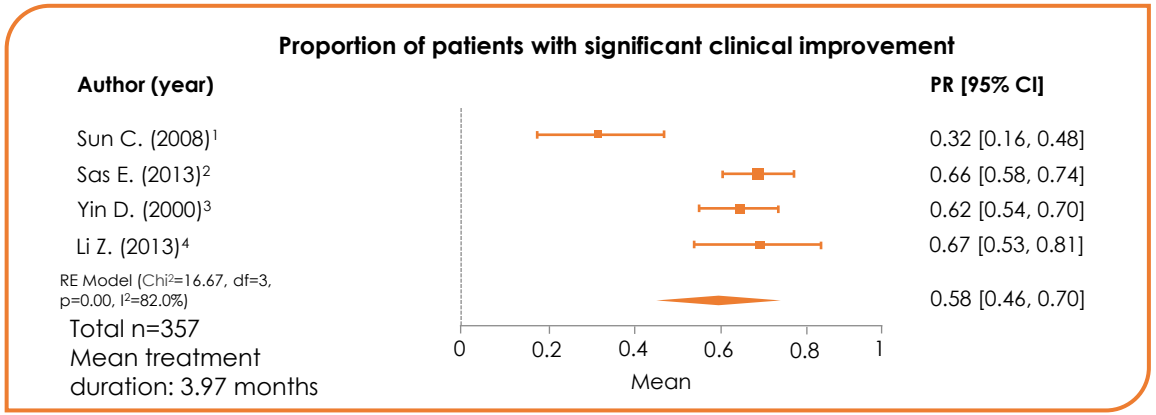
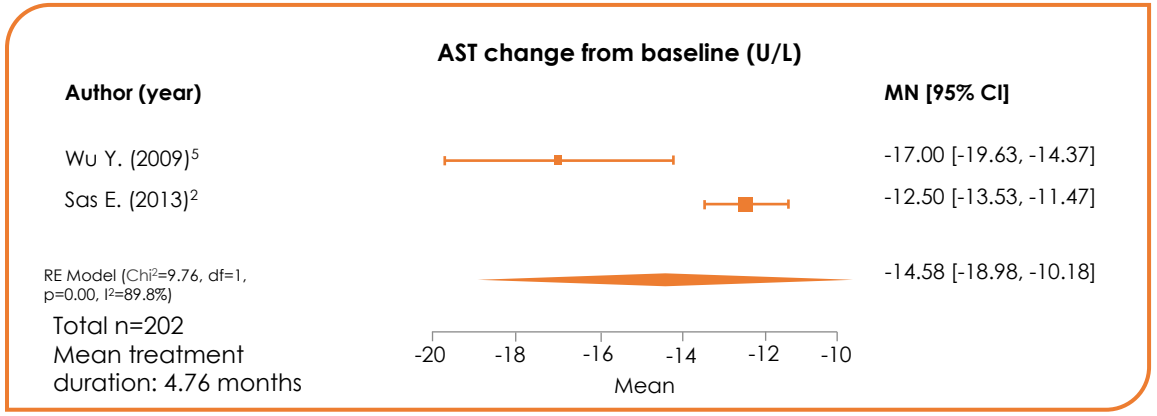
EPLs for NAFLD associated with metabolic syndrome: a systematic review and network meta-analysis (2/3)

Results of a direct meta-analysis of RCTs comparing the effect of treatment with EPLs + AD vs AD alone[6]





The pooled estimate of the proportion of patients showing **significant clinical improvement** was 58%

The pooled change from baseline in **AST** levels was –14.58 U/mL

AD anti-diabetic treatment; AST, aspartate aminotransferase; CI, confidence interval; df, degrees of freedom; EPL, essential phospholipids; MN, raw mean; NAFLD, non-alcoholic fatty liver disease; PR, proportion of responders; RCTs, randomised controlled trials; RE, random effects

1. Sun C, et al. Clin Focus 2008;23:1272–3; 2. Sas E, et al. J Hepatol 2013;58(Suppl 1):S549; 3. Yin D, et al. Med JQ illu 2000;15:277–8; 4. Li Z. J Tradit Chinese Med 2013;31:10–1; 5. Wu Y. J TCM Univ. Hunan 2009;29:41–2; 6. Dajani A, et al. World J Clin Cases 2020;8(21):5235–49

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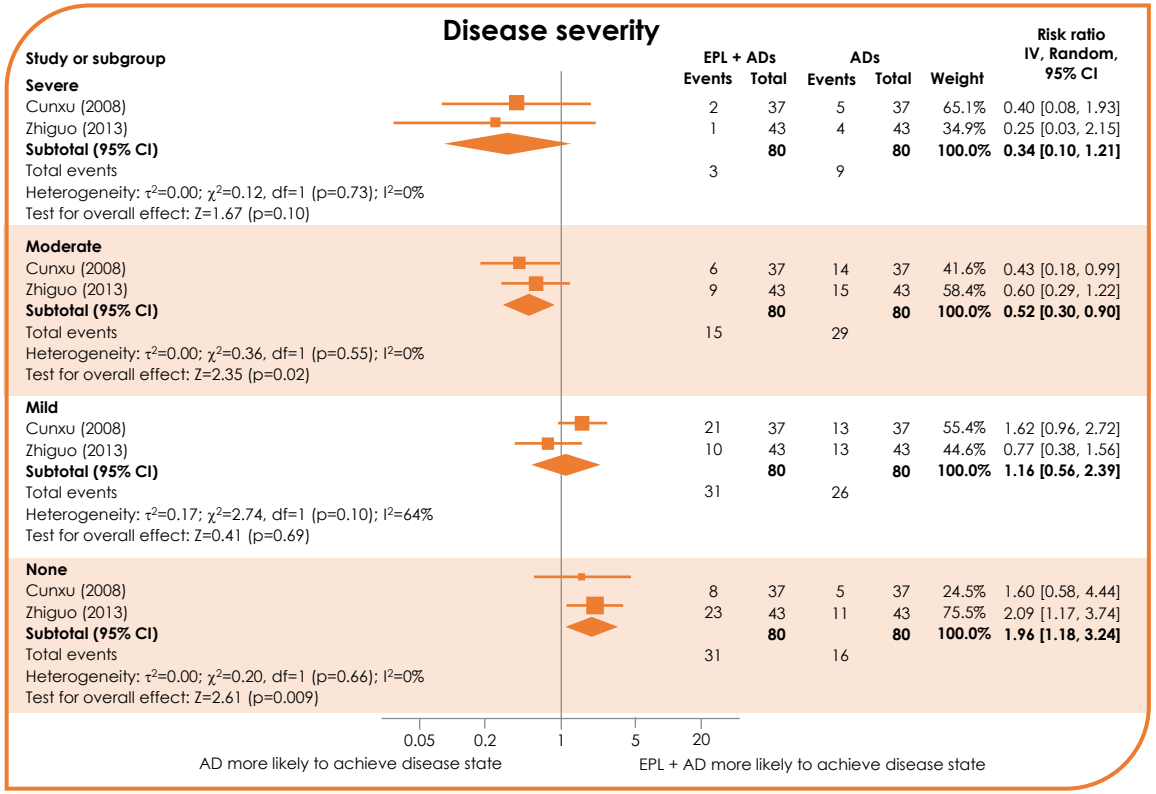
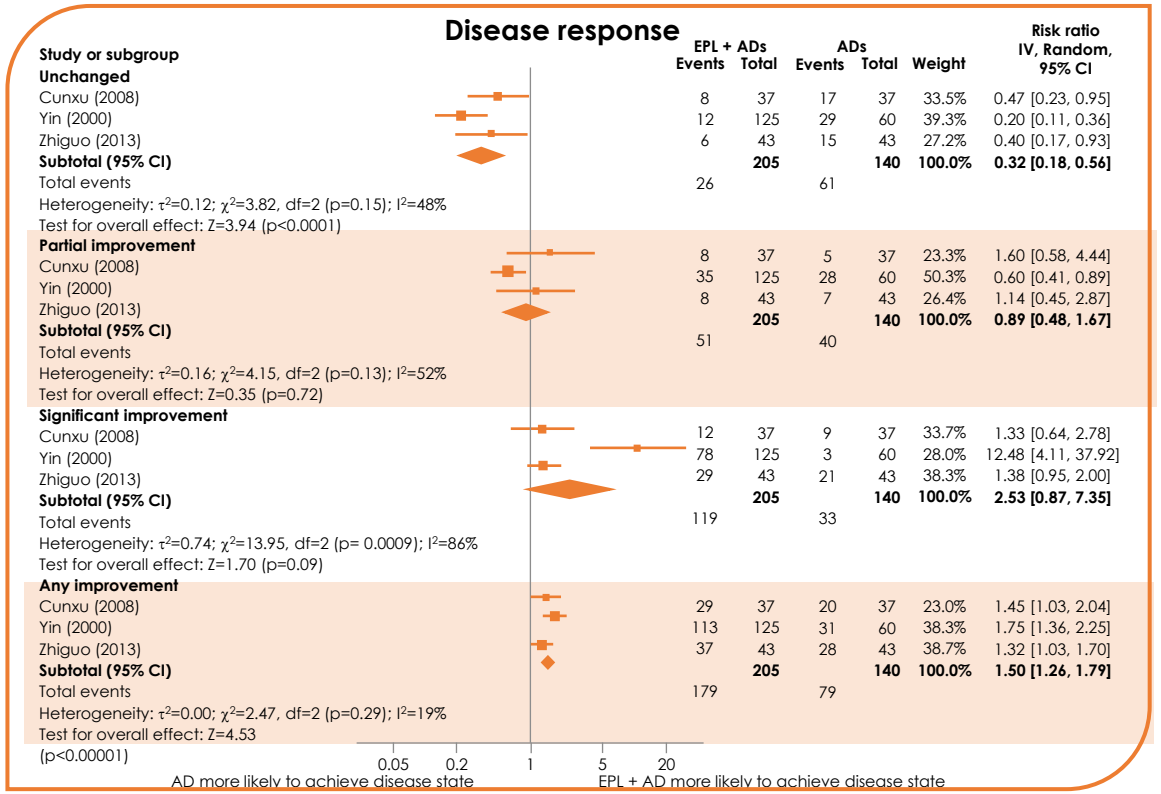
EPLs for NAFLD associated with metabolic syndrome: a systematic review and network meta-analysis (3/3)





AD, anti-diabetic treatment; CI, confidence interval; df, degrees of freedom; EPL, essential phospholipid; NAFLD, non-alcoholic fatty liver disease; IV, inverse variance
Dajani A, et al. World J Clin Cases 2020;8(21):5235–49

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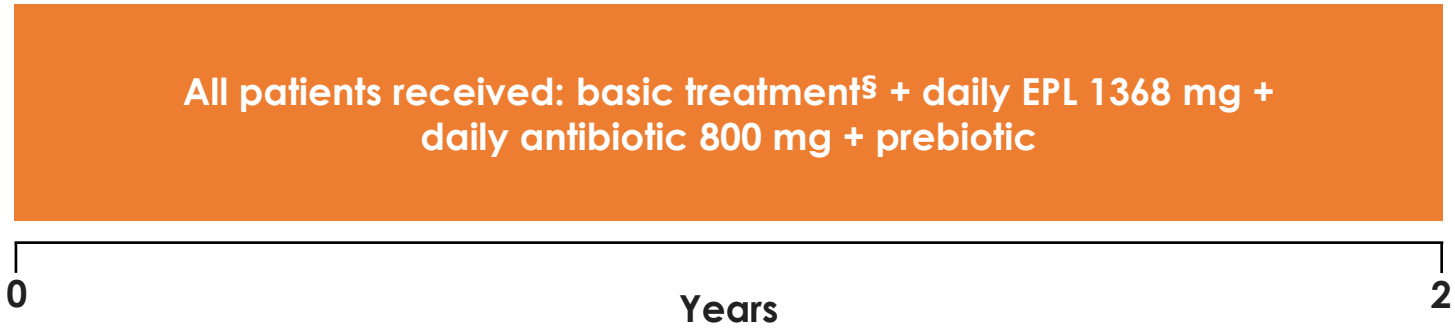
Complex treatment with EPL, antibiotic and prebiotic for patients with treatment-resistant NAFLD: study design

Prospective study investigating the effects of treatment with EPL*, antibiotic† and prebiotic‡ in patients with NAFLD who had not responded to previous therapies

N=46 patients with NAFLD, aged 38–46 years, who had not responded to previous treatment



Primary endpoints: gut microbiota profile, histological findings, ultrasound results, FibroMAX™ test results and disease activity (Metavir score)

*Essentiale® forte N, produced by A Nattermann and Cie GmbH; †Nifuroxazide; ‡Eubicor® (NPC BIC); §Basic treatment included a dietary and physical regimen
EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; γ-GT, gamma glutamyl transferase
Grinevich V, et al. Poster presented at Obesity 2012

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Complex treatment with EPL, antibiotic and prebiotic can slow disease progression in patients with treatment-resistant NAFLD

There was a **positive correlation** between the level of liver **inflammation and concentration of certain gut microbiota**: Alistipes (p<0.048), Faecalibacterium (p<0.02), Catenibacterium (p<0.01), Streptococcus (p<0.03), Peptostreptococcaceae (p<0.03)

In patients with treatment-resistant NAFLD treated with EPL, antibiotic and prebiotic, the **progression of hepatic fibrosis was slower compared with baseline**

After 12 months of treatment with EPL, antibiotic and prebiotic, there was a **significant reduction in liver steatosis (p<0.02) and disease activity (p<0.03)** in patients with NAFLD compared with baseline

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease

Grinevich V, et al. Poster presented at Obesity 2012

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Conclusions

1. EPLs are widely used in liver diseases due to their hepatoprotective effects and can **enhance the management of NAFLD and metabolic comorbidities**
2. Treatment with PUPC improved **liver function and glycaemic control** in patients with T2DM and NASH
3. In patients with ALD, treatment with PUPC improved **liver function and insulin-sensitivity**, as well as **reduced liver steatosis and fibrosis**
4. The results of a systematic review and network meta-analysis demonstrated that **EPL treatment can benefit patients with NAFLD and metabolic comorbidities** such as obesity and T2DM

PUPC refers to phosphatidylcholine molecules carrying essential fatty acids.
ALD, alcoholic liver disease; EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis PUPC, polyunsaturated phosphatidylcholine; T2DM, type 2 diabetes mellitus

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