Advantageously, monitoring for changes in plasma phospholipid levels, preferably PC levels does not require any tedious brain imaging techniques such as electroencephalography (EEG).

Summary of the invention

Through clinical studies the inventors established a set of biomarkers of plasma polar lipid species, preferably phosphatidylcholine [PC] species, which help identifying subjects suffering from impaired levels of these plasma phospholipids, at the basis of which impaired phospholipid levels a subject can be identified having an extremely high likelihood of developing MCI and AD. These biomarkers are thus reliably predictive for conversion of a subject to MCI and AD, and help identifying ant treating preclinical MCI and AD subjects.

In addition, the inventors found that impaired plasma phospholipid levels could be normalized using B vitamins only. Also, B vitamins helped preventing the plasma levels of a set of polar lipids, preferably a set of phospholipids from changing. In a further intervention study of 24 weeks involving administration of a product comprising B vitamins to a subject suffering from mild AD it was found that impaired plasma phospholipid levels could be normalized.

In one aspect, there is provided the use of a preparation for the manufacture of a composition for preventing or treating impaired plasma levels of one or more polar lipids selected from the group consisting of C16:1 CE; C18:3 CE; C20:4 CE; PI(34:1); PI(38:2); PI(38:4); C16:0 CE; C18:2 CE; PA(34:3); PE(36:0); PE(38:0); aePC(36:0); aePC(38:0); aePC(38:4); aePC(40:4); lPC(18:0); lPC(18:3); lPC(20:4); PC(36:1); PC(38:0); PC(38:4); PC(40:4); DSM(18:0); aePC(32:1); aePC(32:2); aePC(34:0); PC(44:2); SM(16:0); SM(18:0); SM(22:0); SM(24:0); SM(24:1); aePC(36:5); aePC(38:5); aePC(40:5); lPC(20:5); lPC(22:5); PC(36:5); PC(38:5); PC(40:5); PI(38:5); PI(40:5); C20:5 CE; C22:6 CE; aePC(38:6); aePC(40:6); aePE(40:6); PC(36:6); PC(38:6); PC(40:6); PC(42:6); PI(40:6); C22:5 CE; aePE(38:6); lPE(22:6); PE(38:6); PE(40:6); PI(38:6); PC(40:7); PC(40:8); PC(42:10); PC(42:7); PC(42:8); PC(42:9); PE(40:7); lPC(22:6); C19:0 CE; C19:1 CE; C20:0 CE; C20:1 CE; C20:3 CE; PE(34:1); PE(34:2); PE(36:1); PE(36:2); PE(36:3); PE(36:4); PE(38:3); PE(38:4); PE(40:4);

PI(36:3); PI(38:3); PS(38:4); aePC(36:1); aePC(38:1); aePC(38:2); aePC(38:3); aePC(40:2); aePC(40:3); lPC(20:3); PC(34:3); PC(36:3); PC(38:1); PC(38:2); PC(40:3); and PE(40:5) in a preclinical Alzheimer's Disease (AD) or mild cognitive impairment (MCI) subject or a subject with a high likelihood of developing AD or MCI, wherein said composition comprises at least one B vitamin selected from the group consisting of vitamin B6, vitamin B12 and vitamin B9.

In another aspect, there is provided the use of a preparation for the manufacture of a composition for preventing or treating impaired plasma levels of one or more phosphatidylcholines [PC] selected from the group consisting of phosphatidylcholine diacyl C36:6 [PC aa C36:6], phosphatidylcholine diacyl C38:0 [PC aa C38:0], phosphatidylcholine diacyl C38:6 [PC aa C38:6], phosphatidylcholine diacyl C40:6 [PC aa C40:6] and phosphatidylcholine acyl-alkyl C40:6 [PC ae C40:6] in a preclinical AD or MCI subject or a subject with a high likelihood of developing AD or MCI, and wherein said subject is to be administered with a composition comprising at least one B vitamin selected from the group consisting of vitamin B6, vitamin B12 and vitamin B9.

In one leg of experiments, the biomarker panel of phospholipids studied involved impaired plasma levels of phosphatidylcholine diacyl C36:6 [PC aa C36:6], phosphatidylcholine diacyl C38:0 [PC aa C38:0], phosphatidylcholine diacyl C38:6 [PC aa C38:6], phosphatidylcholine diacyl C40:6 [PC aa C40:6] and phosphatidylcholine acyl-alkyl C40:6 [PC ae C40:6]. The increase in plasma levels of these phospholipids was most profound. In one aspect, the preferred targeted plasma polar lipids comprise one or more selected from phosphatidylcholine species with multiple double bonds, preferably selected from the group consisting of 36:6, 38:6, 40:6, more preferably at least two of these polyunsaturated PC species. The invention is particularly directed to treating or preventing impaired plasma levels of at least PC aa 40:6 and/or PC ae 40:6, most preferably at least PC aa 40:6.

Claims

1. Use of a preparation for the manufacture of a composition for preventing or treating impaired plasma levels of one or more polar lipids selected from the group consisting of C16:1 CE; C18:3 CE; C20:4 CE; PI(34:1); PI(38:2); PI(38:4); C16:0 CE; C18:2 CE; PA(34:3); PE(36:0); PE(38:0); aePC(36:0); aePC(38:0); aePC(38:4); aePC(40:4); lPC(18:0); lPC(18:3); lPC(20:4); PC(36:1); PC(38:0); PC(38:4); PC(40:4); DSM(18:0); aePC(32:1); aePC(32:2); aePC(34:0); PC(44:2); SM(16:0); SM(18:0); SM(22:0); SM(24:0); SM(24:1); aePC(36:5); aePC(38:5); aePC(40:5); lPC(20:5); lPC(22:5); PC(36:5); PC(38:5); PC(40:5); PI(38:5); PI(40:5); C20:5 CE; C22:6 CE; aePC(38:6); aePC(40:6); aePE(40:6); PC(36:6); PC(38:6); PC(40:6); PC(42:6); PI(40:6); C22:5 CE; aePE(38:6); lPE(22:6); PE(38:6); PE(40:6); PI(38:6); PC(40:7); PC(40:8); PC(42:10); PC(42:7); PC(42:8); PC(42:9); PE(40:7); lPC(22:6); C19:0 CE; C19:1 CE; C20:0 CE; C20:1 CE; C20:3 CE; PE(34:1); PE(34:2); PE(36:1); PE(36:2); PE(36:3); PE(36:4); PE(38:3); PE(38:4); PE(40:4); PI(36:3); PI(38:3); PS(38:4); aePC(36:1); aePC(38:1); aePC(38:2); aePC(38:3); aePC(40:2); aePC(40:3); lPC(20:3); PC(34:3); PC(36:3); PC(38:1); PC(38:2); PC(40:3); and PE(40:5) in a preclinical Alzheimer's Disease (AD) or mild cognitive impairment (MCI) subject or a subject with a high likelihood of developing AD or MCI, wherein said composition comprises at least one B vitamin selected from the group consisting of vitamin B6, vitamin B12 and vitamin B9.

2. Use according to claim 1, said composition comprising at least two B vitamins selected from the group consisting of vitamin B6, vitamin B12 and vitamin B9.

3. Use according to claim 2, said composition comprising vitamin B6, vitamin B12 and vitamin B9.

4. Use of a preparation for the manufacture of a composition for preventing or treating impaired plasma levels of one or more phosphatidylcholines [PC] selected from the group consisting of phosphatidylcholine diacyl C36:6 [PC aa C36:6], phosphatidylcholine diacyl C38:0 [PC aa C38:0], phosphatidylcholine diacyl C38:6 [PC aa C38:6], phosphatidylcholine diacyl C40:6 [PC aa C40:6] and phosphatidylcholine acyl-alkyl C40:6 [PC ae C40:6] in a preclinical AD or MCI subject or a subject with a high likelihood of developing AD or MCI, and wherein said subject is to be administered with a composition comprising at least one B vitamin selected from the group consisting of vitamin B6, vitamin B12 and vitamin B9.

5. Use according to claim 4, said composition comprising at least two B vitamins selected from the group consisting of vitamin B6, vitamin B12 and vitamin B9.

6. Use according to claim 5, said composition comprising vitamin B6, vitamin B12 and vitamin B9.

7. Use according to any one of claim 1 - 6, said composition comprising per daily dosage or per 100 ml, at least one, preferably at least two, most preferably all of:
   0.5 – 10000 µg, preferably 0.5 - 1000 µg vitamin B12;
   0.5 – 100 mg, preferably 0.7- 20 mg vitamin B6; and
   100 – 5000 µg, preferably 150-1000 µg folic acid.

8. Use according to any one of claim 1 - 6, said composition comprising per daily dosage or per 100 ml, 0.5 – 100 mg, preferably 0.7-20 mg vitamin B6, and 100 – 5000 µg, preferably 150-1000 µg folic acid.

9. Use according to any one of claim 1 - 6, wherein the plasma polar lipids are lPC 22:6 and/or PC 40:6, preferably at least lPC 22:6.

10. Use according to any one of claims 4 - 6, wherein said one or more phosphatidylcholines involve at least two, more preferably at least three phosphatidylcholine species selected from the group consisting of phosphatidylcholine diacyl C36:6 [PC aa C36:6], phosphatidylcholine diacyl C38:0 [PC aa C38:0], phosphatidylcholine diacyl C38:6 [PC aa C38:6], phosphatidylcholine diacyl C40:6 [PC aa C40:6] and phosphatidylcholine acyl-alkyl C40:6 [PC ae C40:6].

11. Use according to any one of claims 4 - 6, wherein said one or more phosphatidylcholine species is selected from the group consisting of phosphatidylcholine diacyl C36:6 [PC aa C36:6], phosphatidylcholine diacyl C38:6 [PC aa C38:6], phosphatidylcholine diacyl C40:6 [PC aa C40:6] and phosphatidylcholine acyl-alkyl C40:6 [PC ae C40:6], preferably at least phosphatidylcholine diacyl C40:6 [PC aa C40:6] and/or phosphatidylcholine acyl-alkyl C40:6 [PC ae C40:6].

12. Use according to any one of claims 4 - 6, wherein said plasma PC levels are monitored in said subject before and/or after administration.

13. Use according to any one of the preceding claims, wherein said composition further comprises one or more of uridine and cytidine, or salts, phosphates, acyl derivatives or esters thereof.

14. Use according to any one of the preceding claims, wherein said composition further comprises a lipid fraction comprising at least one of docosahexaenoic acid (22:6; DHA), eicosapentaenoic acid (20:5; EPA) and docosapentaenoic acid (22:5; DPA), or esters thereof.

15. Use according to any one of the preceding claims, wherein said composition further comprises, per daily dose or preferably per 100 ml composition, at least 500

mg of DHA, preferably at least 600 mg of DHA, and at least 50 mg of uridine, preferably at least 100 mg of uridine.

16. Use according to any one of the preceding claims, wherein the composition comprises, per daily dose or preferably per 100 ml composition:

0.5 – 10000 µg, preferably 0.5 - 1000 µg vitamin B12;
0.5 – 100 mg, preferably 0.7- 20 mg vitamin B6;
100 – 5000 µg, preferably 150-1000 µg folic acid;
100 – 500 mg, preferably 200-400 mg EPA,
1000 – 1500 mg, preferably 1100-1300 mg DHA,
50 – 600 mg, preferably 60-200 mg phospholipids,
200 – 600 mg, preferably 300-500 mg choline,
400 – 800 mg, preferably 500-700 mg UMP (uridine monophosphate),
20 – 60 mg, preferably 30-50 mg vitamin E (alpha-TE),
60 – 100 mg, preferably 70-90 mg vitamin C, and
40 – 80 µg, preferably 50-70 µg selenium.

17. Use according to any one of the preceding claims, wherein the subject is an elderly of at least 50 years of age, and not suffering from any cognitive deficits.