[0006] There remains a need for methods and compositions useful to treat or prevent obesity and related diseases, in particular GDM. There is also a need for methods and compositions for treating or preventing GDM which does not rely changes in dietary modification and counselling. Methods and compositions for the prevention or amelioration of GDM-associated risks or sequelae of GDM are also desirable.

[0007] It is an object of this invention to provide improved or alternative methods and compositions for treating or preventing GDM and/or treating or preventing one or more GDM-associated risks or one or more sequelae of GDM.

SUMMARY

[0008] In one aspect, the present disclosure relates to use of one or more polar lipids in the manufacture of a medicament for treating or preventing gestational diabetes mellitus (GDM) or at least one GDM-associated risk or sequelae of GDM in a subject, comprising that the medicament is to be administered to a subject in need thereof.

[0008a] In another aspect, the present disclosure relates to use of one or more polar lipids in the manufacture of a medicament for treating or preventing at least one GDM-associated risk or sequelae of GDM in a foetal, neonatal, infant or child subject, comprising that the medicament is to be administered to the mother of the foetal, neonatal, infant or child subject in need thereof.

[0008b] In one example, the disclosure relates to a method of treating or preventing GDM in a subject in need thereof, and/or treating or preventing one or more GDM-associated risks or one or more sequelae of GDM in a subject in need thereof, the method comprising administration of one or more polar lipids to the subject.

[0009] In another example, the disclosure relates to a method of treating or preventing GDM in a subject in need thereof, the method comprising administration of one or more polar lipids to the subject.

[0010] In another example, the disclosure relates to a method of treating or preventing one or more GDM-associated risks or one or more sequelae of GDM in a subject in need thereof, the method comprising administration of one or more polar lipids to the subject.

[0011] In another example, the disclosure relates to a method of treating or preventing at least one GDM-associated risk or sequelae of GDM in a foetal, neonatal,

infant or child subject, the method comprising administration of one or more polar lipids to the mother of the foetal, neonatal, infant or child subject in need thereof.

[0012] In another example, the disclosure relates to one or more polar lipids for treating or preventing GDM, and/or for treating or preventing one or more GDM-associated risks or one or more sequelae of GDM.

[0013] In another example, the disclosure relates to a composition comprising one or more polar lipids for treating or preventing GDM, or for treating or preventing one or more GDM-associated risks or one or more sequelae of GDM.

[0014] In another example, the disclosure relates to use of one or more polar lipids in the manufacture of a composition or medicament for treating or preventing GDM, and/or for treating or preventing one or more GDM-associated risks or one or more sequelae of GDM.

[0015] In another example, the disclosure relates to a method of lowering fasting mean blood glucose levels in a subject, the method comprising administering an effective amount of one or more polar lipids to a subject in need thereof.

[0016] In other examples, the disclosure relates to use of compositions of the disclosure to reduce the risk of developing diabetes during pregnancy, reduce fasting blood sugar/glucose during pregnancy, reduce fasting blood glucose, maintain a normal blood sugar during pregnancy, and/or maintain normal blood glucose concentrations during pregnancy, and methods of achieving same.

[0017] Any of the following examples may relate to any of the above examples, alone or in any combination.

[0018] In various examples, the one or more polar lipids may be administered in the form of a composition with a physiologically acceptable diluent, adjuvant, carrier or excipient.

[0019] In various examples, the physiologically acceptable diluent, adjuvant, carrier or excipient may be a nutritional composition. In one example, the nutritional composition is cultured milk, yoghurt, cheese, ice cream, bar, milk drink or milk powder.

[0020] In various examples, the composition may be a pharmaceutical composition or supplement and said excipient or diluent is pharmaceutically acceptable diluent, adjuvant, carrier or excipient.

[0021] In various examples, the one or more polar lipids may be derived from non-human mammalian milk. In various examples, the one or more polar lipids may consist of or consist essentially of polar lipids derived from non-human mammalian milk. In various examples, the non-human mammalian milk may be sheep, goat, pig, mouse, water buffalo, camel, yak, horse, donkey, llama, or bovine milk. Preferred is bovine milk.

[0022] In various examples, the one or more polar lipids may comprise one or more phospholipids, one or more gangliosides, one or more ceramides, one or more cerebrocides, milk fat globule membrane (MFGM) material, or any combination of any two or more thereof. In various examples, the method may comprise administration of milk fat globule membrane material comprising the one or more polar lipids.

[0023] In various examples, the one or more gangliosides may comprise one or more glycosphingolipids, GD1, GD2, GD3, GM1, GM2, GM3, one or more monosialogangliosides, one or more disialogangliosides, or one or more polysialogangliosides, or any combination of any two or more thereof. In various examples, the one or more gangliosides may comprise GD3 or GM3, or a combination thereof.

[0024] In various examples, the one or more phospholipids may comprise one or more glycerolphospholipids, one or more phosphatidylcholines, one or more phosphatidylinositols, one or more phosphatidylserines, one or more phosphatidylethanolamines, one or more sphingomyelins, one or more dihydrosphingomyelins, one or more lysophospholipids, one or more phosphatidylglycerols, or any combination of any two or more thereof.

[0025] In various examples, at least about 60, 70, 80, 85, 90, 95, 99 or 100% of the fatty acids in the one or more phosphatidylcholines may be C14:0 or longer, each fatty acid optionally comprising one or more, two or more, three or more, or four or more double bonds in the main carbon chain of the fatty acid, and useful ranges may be selected between any of these values (for example, about 60 to about 100%). In various examples, the one or more phosphatidylcholines may be obtained solely from milk fat, preferably bovine milk fat. In various examples, the composition may comprise one or more phosphatidylcholines and one or more non-phosphatidylcholine polar lipids.

[0026] In various examples, the one or more lysophospholipids may comprise one or more lysophosphatidylcholines, one or more lysophosphatidylserines, one or more lysophosphatidylethanolamines, one or more lysophosphatidylinositols, or any

combination of any two or more thereof. In various examples, the one or more sphingomyelins may comprise sphingomyelin, dihydrosphingomyelin, or a combination thereof. In various examples, the one or more glycerolphospholipids may comprise phosphatidylglycerol.

[0027] In various examples, the composition may comprise phosphatidic acid.

[0028] In various examples, the one or more polar lipids may be obtained solely from bovine milk fat.

[0029] In various examples, the composition may comprise at least about 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, or 70% by weight polar lipid, and useful ranges may be selected between any of these values (for example, about 0.01 to about 2, about 0.01 to about 5, about 0.01 to about 10, about 0.01 to about 15, about 0.01 to about 20, about 1 to about 5, about 1 to about 10, about 1 to about 15, about 1 to about 20, about 0.01 to about 70, or about 1 to about 70%).

[0030] In various examples, the composition may comprise at least about 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, or 70% by weight phospholipids, and useful ranges may be selected between any of these values (for example, about 0.01 to about 2, about 0.01 to about 5, about 0.01 to about 10, about 0.01 to about 15, about 0.01 to about 20, about 1 to about 5, about 1 to about 10, about 1 to about 15, about 1 to about 20, about 0.01 to about 70, or about 1 to about 70%).

[0031] In various examples, the composition may comprise at least about 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, or 70% by weight milk fat globule membrane material, and useful ranges may be selected between any of these values (for example, about 0.01 to about 2, about 0.01 to about 5, about 0.01 to about 10, about 0.01 to about 15, about

0.01 to about 20, about 1 to about 5, about 1 to about 10, about 1 to about 15, about 1 to about 20, about 0.01 to about 70, or about 1 to about 70%).

[0032] In various examples, the composition may comprise

a) about 0.01 to about 0.5%, preferably about 0.02 to about 0.2% by weight of one or more phosphatidylcholines,

b) about 0.005 to about 0.07%, preferably about 0.008 to about 0.05% by weight of one or more phosphatidylinositols,

c) about 0.005 to about 0.07%, preferably about 0.008 to about 0.05% by weight of one or more phosphatidylserines,

d) about 0.01 to about 0.5%, preferably about 0.02 to about 0.2% by weight of one or more phosphatidylethanolamines,

e) about 0.01 to about 0.1%, preferably about 0.02 to about 0.08% by weight sphingomyelin,

f) 0.001 to about 0.05%, preferably 0.001 to about 0.02% by weight dihydrosphingomyelin,

g) any combination of any two or more of a) to f).

[0033] In various examples, the one or more polar lipids, or one or more phospholipids may comprise from about 0.01% to about 5% by weight of the total lipid in the composition.

[0034] In various examples, the total phospholipid in the composition may comprise

a) about 20 to about 40%, preferably about 25 to about 30% by weight of one or more phosphatidylcholines,

b) about 5 to about 20%, preferably about 7 to about 12% by weight of one or more phosphatidylinositols,

c) about 5 to about 20%, preferably about 7 to about 12% by weight of one or more phosphatidylserines,

d) about 15 to about 40%, preferably about 20 to about 30% by weight of one or more phosphatidylethanolamines,

e) about 10 to about 30%, preferably about 15 to about 20% by weight sphingomyelin,

f) about 0.5 to about 15%, preferably about 1 to about 5% by weight dihydrosphingomyelin, or

g) any combination of any two or more of a) to f).

[0035] In various examples, the composition may comprise from about 2 to about 10 mg gangliosides per serve. In various examples, the composition may provide from about 2 to about 20 mg gangliosides per day.

[0036] In various examples, the composition may comprise from about 0.3 to about 6 mg gangliosides per gram of the composition.

[0037] In various examples, the composition may comprise from about 5 to about 35 mg per 100 g, preferably about 10 to about 20 mg per 100 g gangliosides. In various examples, the gangliosides may comprise 50-100% by weight GD3 and 1-60% GM3.

[0038] In various examples, the composition may comprise from about 0.1 to about 5 g phospholipids per serve. In various examples, the composition may provide from about 0.1 to about 10 g phospholipids per day.

[0039] In various examples, the method may comprise administering to the subject from about 0.1 to about 15 g of the one or more polar lipids per day.

[0040] In various examples, the method may comprise administering to the subject from about 2 to about 20 mg gangliosides per day.

[0041] In various examples, the method may comprise administering to the subject from about 0.1 to about 10 g phospholipids per day.

[0042] In various examples, where the subject is a foetal subject, the method of treating or preventing one or more GDM-associated risks or one or more sequelae of GDM may comprise administering the one or more polar lipids or a composition comprising the polar lipids to the foetal subject's mother. It will be appreciated that in such examples, the administration to the subject may be considered indirect administration. In various examples, the composition may be a maternal formula or a maternal supplement.

[0043] In various examples, where the subject is a neonatal, an infant, or a child subject, the method of treating or preventing one or more GDM-associated risks or one or more sequelae of GDM may comprise administering a composition comprising the one or more polar lipids to the subject. It will be appreciated that in such examples, the administration to the subject may be considered direct administration.

[0044] In various examples, such as where the subject is a breastfeeding neonatal, infant, or child subject, the method of treating or preventing one or more GDM-

associated risks or one or more sequelae of GDM may comprise administering the one or more polar lipids or a composition comprising the one or more polar lipids to the subject's mother. It will be appreciated that in such examples, the administration to the subject may be considered indirect administration.

[0045] In various examples, the composition may be a formula, for example a maternal formula, infant formula, follow-on formula, growing-up formula or dietetic product, including hypoallergenic examples of such compositions.

[0046] In preferred examples where the subject is an adult subject, the method comprises administering a composition comprising the one or more polar lipids to the subject. Preferably, the composition is a supplement, or nutritional composition such as a formula, dietetic product or food. It will be understood that in such examples the subject is a woman, particularly a woman who has had one or more previous pregnancies, a pregnant woman, or a breast-feeding woman.

[0047] In various examples, the composition may be suitable for oral administration. In various examples, the composition may be suitable for parenteral administration. In various examples relating to preventing one or more GDM-associated risks or one or more sequelae of GDM in a foetal subject, the composition may be suitable for oral administration to a pregnant mother during gestation.

[0048] In various examples, the method may be a method of treating or preventing GDM in a subject having an increased risk of GDM. In one example, the method may be a method of treating or preventing GDM in a subject who has previously suffered GDM. In one example, the method may be a method of treating or preventing GDM in a subject over the age of 35 years, for example, a subject over the age of 35 years at conception. In another example, the method may be a method of treating or preventing GDM in a subject who has previously been pregnant.

[0049] In various examples, the subject may have a BMI of less than 25 or 30 kg/m2. In various examples, the subject may have a BMI of greater than 25 (overweight) or 30 (obese) kg/m2. In various examples, the subject may have high blood pressure. In various examples, the subject may have prediabetes. In various examples, the subject may be a woman, a woman who has had one or more previous pregnancies, a pregnant woman, or a breast-feeding woman.

[0050] In various examples, the method may be a method of preventing recurrence of GDM in a subject who has previously suffered from GDM, the method comprising administering an effective amount of one or more polar lipids to a subject in need thereof.

[0051] In various examples, the method may comprise beginning administration of the one or more polar lipids after the first trimester of pregnancy. In various examples, administration of the one or more polar lipids may begin at about 14 to about 16 week's gestation.

[0052] In various examples, such as in a method of lowering fasting mean blood glucose levels in a subject, the fasting mean blood glucose level may be below about 5.5 mmol/L, preferably about 4.35 mmol/L.

[0053] In various examples, treating or preventing the at least one GDM-associated risks or sequelae of GDM may comprise preventing or reducing one or more of the risks or sequalae disclosed herein, including excessive birth weight, preterm birth, unwanted induced labour, suboptimal APGAR score at birth, infant hypoglycaemia, and infant respiratory distress syndrome at birth. In this context, it should be understood that reducing the risk or sequalae may include a reduction in the risk of, a reduction in the incidence, and/or a reduction in the magnitude of the risk or of the sequalae.

[0054] In various examples, the composition may further comprise, or the method may further comprise separate, simultaneous, or sequential administration of, or the polar lipids may be used separately, simultaneously, or sequentially with, a probiotic or a killed or attenuated probiotic, or any combination of any two or more thereof. Preferably the probiotic is *Lactobacillus rhamnosus* HN001.

[0055] The term "comprising" as used in this specification means "consisting at least in part of". When interpreting each statement in this specification that includes the term "comprising", features other than that or those prefaced by the term may also be present. Related terms such as "comprise" and "comprises" are to be interpreted in the same manner.

[0056] It is intended that reference to a range of numbers disclosed herein (for example, 1 to 10) also incorporates reference to all rational numbers within that range (for example, 1, 1.1, 2, 3, 3.9, 4, 5, 6, 6.5, 7, 8, 9 and 10) and also any range of rational numbers within that range (for example, 2 to 8, 1.5 to 5.5 and 3.1 to 4.7) and,

therefore, all sub-ranges of all ranges expressly disclosed herein are hereby expressly disclosed. These are only examples of what is specifically intended and all possible combinations of numerical values between the lowest value and the highest value enumerated are to be considered to be expressly stated in this application in a similar manner.

[0057] In this specification where reference has been made to patent specifications, other external documents, or other sources of information, this is generally for the purpose of providing a context for discussing the features of the disclosure. Unless specifically stated otherwise, reference to such external documents is not to be construed as an admission that such documents, or such sources of information, in any jurisdiction, are prior art, or form part of the common general knowledge in the art.

[0058] This disclosure may also be said broadly to consist in the parts, elements and features referred to or indicated in the specification of the application, individually or collectively, and any or all combinations of any two or more said parts, elements or features, and where specific integers are mentioned herein which have known equivalents in the art to which this disclosure relates, such known equivalents are deemed to be incorporated herein as if individually set forth.

DETAILED DESCRIPTION OF THE INVENTION

[0059] The present invention recognises for the first time the beneficial effects of administration of polar lipids, preferably polar lipids derived from milk, on the incidence and severity of GDM.

[0060] Accordingly, in a first aspect the invention provides a method of treating or preventing GDM in a subject, the method comprising administration of one or more polar lipids to a subject in need thereof.

[0061] In a further aspect, the invention also provides a method of treating or preventing GDM-associated risks or sequelae of GDM in a subject, the method comprising administration of polar lipids to a subject in need thereof. GDM-associated risks in a pregnant subject are, for example but not limited to high blood pressure, urinary tract infections, unwanted induced labour, caesarean birth, and increased risk of type-2 diabetes. GDM-associated risks or sequelae of GDM in a foetal, neonatal, infant, child or adult subject (in particular, subjects whose birth mother suffered from GDM during their period *in utero*) are, for example but not limited to excessive birth weight, suboptimal APGAR ("Appearance, Pulse, Grimace, Activity, and Respiration") score at

birth, infant hypoglycaemia, preterm birth, shoulder dystocia, macrosomia, congenital defects including impaired cognitive development, and neonatal complications such as hypoglycaemia, jaundice and respiratory distress, type 2 diabetes, cardiovascular disease, obesity and metabolic issues.

[0062] While various routes and methods of administration are contemplated, oral administration of polar lipids, such as in a composition suitable for oral administration, is

CLAIMS

1. Use of one or more polar lipids in the manufacture of a medicament for treating or preventing gestational diabetes mellitus (GDM) or at least one GDM-associated risk or sequelae of GDM in a subject, comprising that the medicament is to be administered to a subject in need thereof.

2. Use of one or more polar lipids in the manufacture of a medicament for treating or preventing at least one GDM-associated risk or sequelae of GDM in a foetal, neonatal, infant or child subject, comprising that the medicament is to be administered to the mother of the foetal, neonatal, infant or child subject in need thereof.

3. The use of claim 1 or 2 wherein the one or more polar lipids is to be administered in a composition comprising a physiologically acceptable diluent, adjuvant, carrier or excipient.

4. The use of any one of claims 1 to 3 wherein the one or more polar lipids is to be administered in a composition comprising, or in the form of, a food, preferably a food selected from cultured milk, yoghurt, cheese, milk drink and milk powder; or wherein the one or more polar lipids is to be administered in a pharmaceutical composition comprising a pharmaceutically acceptable diluent, adjuvant, carrier or excipient.

5. The use of any one of claims 1 to 3 wherein the one or more polar lipids is to be administered in at least one of: a maternal formula, a maternal supplement, a dietetic product, an infant formula, a follow-on formula, and a growing-up formula.

6. The use of any one of claims 1 to 5 wherein the one or more polar lipids is derived from non-human mammalian milk, preferably bovine milk.

7. The use of any one of claims 1 to 6 wherein the one or more polar lipids comprise one or more phospholipids, one or more gangliosides or a combination thereof.

8. The use of claim 7 wherein the one or more gangliosides comprises GD3, GM3 or a combination thereof.

9. The use of claim 7 or 8 wherein the one or more phospholipids comprises one or more phosphatidylcholines, one or more phosphatidylinositols, one or more phosphatidylserines, one or more lysophospholipids, one or more phosphatidylethanolamines, one or more sphingomyelins, one or more

dihydrosphingomyelins, one or more glycerolphospholipids, phosphatidylglycerol, or a combination of any two or more thereof.

10. The use of any one of claims 1 to 9 wherein the subject, or the mother of the foetal, neonatal, infant or child subject, has an increased risk of GDM.

11. The use of claim 10 wherein the subject, or mother, has previously suffered GDM.

12. The use of claim 10 or 11 wherein the subject, or mother, over the age of 35 years.

13. The use of any one of claims 10 to 12 wherein the subject, or mother, has previously been pregnant.

14. The use of any one of claims 1 to 9 wherein the subject is a woman, a woman who has had one or more previous pregnancies, a pregnant woman, or a breast-feeding woman, with a BMI of less than 25 or 30 kg/m^2.

15. The use of any one of claims 1 to 9 wherein the subject is a woman, a woman who has had one or more previous pregnancies, a pregnant woman, or a breast-feeding woman, with a BMI of greater than 25 or 30 kg/m^2.

16. The use of any one of claims 1 to 15 wherein the subject is a woman, a woman who has had one or more previous pregnancies, a pregnant woman, or a breast-feeding woman, with high blood pressure.

17. The use of any one of claims 1 to 16 wherein the subject is a woman, a woman who has had one or more previous pregnancies, a pregnant woman, or a breast-feeding woman, with prediabetes.

18. The use of any one of claims 1 to 17 in wherein administration of the one or more polar lipids commences after the first trimester of pregnancy, preferably wherein administration commences between 14 – 16 weeks gestation.

19. The use of any one of claims 1 to 18 comprising lowering fasting mean blood glucose levels in the subject, or the mother of the foetal, neonatal, infant or child subject, preferably to less than about 4.35 mmol/l.

20. The use of any one of claims 1 to 19 wherein the treating or preventing comprises administration of milk fat globule membrane material comprising the one or more polar lipids; and/or wherein the treating or preventing further comprises separate, simultaneous, or sequential administration of a probiotic, preferably *Lactobacillus rhamnosus* HN001.