[0006] There remains a need for methods and compositions useful to treat or prevent obesity and related diseases, in particular GDM, and particularly methods and compositions utilizing or comprising other lactobacilli. 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 go some way towards achieving one or more of these desiderata or at least to offer the public a useful choice.

SUMMARY OF THE INVENTION

[0008] The disclosure provides a method of treating or preventing GDM in a subject, the method comprising administration of *Lactobacillus rhamnosus* HN001, AGAL deposit number NM97/09514 dated 18 August 1997 to a subject in need thereof.

[0009] In one example, the *L. rhamnosus* HN001 is administered in the form of a composition with a physiologically acceptable diluent, adjuvant, carrier or excipient.

[0010] In one example, HN001 is the only probiotic bacteria administered.

[0011] In one example, HN001 is administered with one or more prebiotics.

[0012] In one example, said physiologically acceptable diluent, adjuvant, carrier or excipient is a food. In one example, the food is cultured milk, yoghurt, cheese, milk drink or milk powder.

[0013] Alternatively the composition is a pharmaceutical composition and said excipient or diluent is pharmaceutically acceptable diluent, adjuvant, carrier or excipient.

[0014] The disclosure also provides a method of treating or preventing one or more GDM-associated risks or one or more sequelae of GDM in a subject, the method comprising administration of *Lactobacillus rhamnosus* HN001, AGAL deposit number NM97/09514 dated 18 August 1997 to a subject in need thereof.

[0015] In 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 comprises administering the *L. rhamnosus* HN001 or a composition comprising *L. rhamnosus* HN001 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 one example, the composition is a maternal formula or a maternal supplement.

[0016] In certain 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 comprises administering a composition comprising *L. rhamnosus* HN001 to the subject. It will be appreciated that in such examples, the administration to the subject may be considered direct administration.

[0017] In other 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 comprises administering the *L. rhamnosus* HN001 or a composition comprising *L. rhamnosus* HN001 to the subject's mother. It will be appreciated that in such examples, the administration to the subject may be considered indirect administration.

[0018] The composition may be a formula, for example a maternal formula follow-on formula, growing-up formula or dietetic product, including hypoallergenic examples of such compositions.

[0019] In preferred examples where the subject is an adult subject, the method comprises administering a composition comprising *L. rhamnosus* HN001 to the subject. Preferably, the composition is a supplement, formula, dietetic product or food.

[0020] In certain examples, the *L. rhamnosus* HN001 is in a reproductively viable form, preferably in a reproductively viable form and amount. In other examples, the *L. rhamnosus* HN001 is killed, lysed, fractionated or attenuated.

[0021] The disclosure further provides *L. rhamnosus* HN001, or a derivative thereof, for treating or preventing GDM, or for treating or preventing one or more GDM-associated risks or one or more sequelae of GDM, and *L. rhamnosus* HN001, or a derivative thereof, in the manufacture of a composition for treating or preventing GDM or for treating or preventing one or more GDM-associated risks or one or more sequelae of GDM. The composition may be a composition such as those as described below including, for example, a food or medicament.

[0022] It will be appreciated that the disclosure also contemplates the use of *L. rhamnosus* HN001 in the manufacture of a composition of the disclosure, for example a composition for treating or preventing GDM in a subject.

[0022a] In one aspect, the disclosure relates to use of *L. rhamnosus* HN001, AGAL deposit number NM97/09514 dated 18 August 1997, in the manufacture of a composition or medicament for treating or preventing gestational diabetes mellitus (GDM), or one or more GDM-associated risks or one or more sequelae of GDM in an adult female subject, and wherein the fasting mean blood glucose level is lowered in the subject to less than about 4.35 mmol/l.

[0022b] In another aspect, the disclosure relates to use of *L. rhamnosus* HN001, AGAL deposit number NM97/09514 dated 18 August 1997, in the manufacture of a composition or medicament for preventing one or more GDM-associated risks or one or more sequelae of GDM in a foetal, neonatal, infant or child subject, wherein the preventing comprises administration of the composition or medicament to the pregnant mother of the foetal, neonatal, infant or child subject during gestation, and wherein the fasting mean blood glucose level is lowered in the pregnant mother of the foetal, neonatal, infant or child subject to less than about 4.35 mmol/l.

[0023] In one example the composition is suitable for oral administration. In other examples, the composition is suitable for parenteral administration. In examples relating to preventing one or more GDM-associated risks or one or more sequelae of GDM in a foetal subject, the composition is suitable for oral administration to a pregnant mother during gestation.

[0024] In various examples, the method is a method of treating or preventing GDM in a subject having an increased risk of GDM. In one example, the method is a method of treating or preventing GDM in a subject who has previously suffered GDM. In one example, the method is a method of treating or preventing GDM in an subject over the age of 35 years, for example, a subject over the age of 35 years at conception. In another example, the method is a method of treating or preventing GDM in a subject who has previously been pregnant.

[0025] In various examples, the subject has a BMI of less than 30 kg/m2.

[0026] In one example, the method is a method of preventing recurrence of GDM in a subject who has previously suffered from GDM, the method comprising administering an effective amount of HN001 or a derivative thereof to a subject in need thereof.

[0027] In one example, the method comprises beginning administration of HN001 after the first trimester of pregnancy. In one example, administration of HN001 begins between 14 – 16 weeks gestation.

[0028] The disclosure also relates to a method of lowering fasting mean blood glucose levels in a subject, the method comprising administering an effective amount of HN001 or a derivative thereof to a subject in need thereof.

[0029] In one example, the fasting mean blood glucose level is below about 4.35 mmol/l.

[0030] 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.

[0031] 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.

[0032] 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 invention. 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] Figure 1 is a diagram of the status of study participants through the trial

[0034] Figure 2 shows the HN001 associations with GDM stratified by A) Age ≥35 years vs <35 years B) BMI ≥ 30 kg/m^2 vs <30 kg/m^2 C) History of GDM D) Systemic antibiotic use since enrolment.

[0035] Figure 3 shows plots of prevalence of GDM by subgroup. The left plot shows the effect of HN001 administration on subjects who had previously been pregnancy vs those who had not (parity, left), and the right plot shows the effect of HN001 administration on subjects over 35 vs those under 35 (maternal age, right).

DETAILED DESCRIPTION OF THE INVENTION

[0036] The present invention recognises for the first time the beneficial effects of administration of the lactic acid bacteria *L. rhamnosus* HN001 on the incidence and severity of GDM.

[0037] Accordingly, in a first aspect the invention provides a method of treating or preventing GDM in a subject, the method comprising administration of *Lactobacillus rhamnosus*

CLAIMS

1. Use of *L. rhamnosus* HN001, AGAL deposit number NM97/09514 dated 18 August 1997, in the manufacture of a composition or medicament for treating or preventing gestational diabetes mellitus (GDM), or one or more GDM-associated risks or one or more sequelae of GDM in an adult female subject, and wherein the fasting mean blood glucose level is lowered in the subject to less than about 4.35 mmol/l.

2. Use of *L. rhamnosus* HN001, AGAL deposit number NM97/09514 dated 18 August 1997, in the manufacture of a composition or medicament for preventing one or more GDM-associated risks or one or more sequelae of GDM in a foetal, neonatal, infant or child subject, wherein the composition or medicament is to be administered to the pregnant mother of the foetal, neonatal, infant or child subject during gestation, and wherein the fasting mean blood glucose level is lowered in the pregnant mother of the foetal, neonatal, infant or child subject to less than about 4.35 mmol/l.

3. The use of claim 1 or 2, wherein the composition or medicament comprises a physiologically acceptable diluent, adjuvant, carrier or excipient.

4. The use of any one of claims 1-3, wherein the composition is or comprises a food, or the composition is or comprises a food selected from cultured milk, yoghurt, cheese, milk drink and milk powder.

5. The use of any one of claims 1-4, wherein the composition or medicament is
   (1) a pharmaceutical composition comprising a pharmaceutically acceptable diluent, adjuvant, carrier or excipient,
   (2) a maternal formula or a maternal supplement, or
   (3) a supplement, formula, dietetic product or food.

6. The use of any one of claims 1-5, wherein the *L. rhamnosus* HN001 is in a reproductively viable form.

7. The use of any one of claims 1-5, wherein the *L. rhamnosus* HN001 is killed, lysed, fractionated or attenuated.

8. The use of any one of claims 1-7, wherein the adult female subject, or the mother of a foetal, neonatal, infant or child subject, has an increased risk of GDM.

9. The use of claim 8, wherein the adult female subject, or the mother of a foetal, neonatal, infant or child subject, has previously suffered GDM, and/or has been previously been pregnant.

10. The use of any one of claims 1-9, wherein
    a. the *L. rhamnosus* HN001, the composition or the medicament is to be administered after the first trimester of pregnancy,
    b. the *L. rhamnosus* HN001, the composition or the medicament is to be administered between 14 – 16 weeks gestation,
    c. the *L. rhamnosus* HN001, the composition or the medicament is to be administered from 14 to 16 weeks gestation until delivery, or
    d. the *L. rhamnosus* HN001, the composition or the medicament is to be administered from 14 to 16 weeks gestation to 6 months post-partum.

11. The use of any one of claims 1-11, wherein
    a. the treatment is prophylactic treatment,
    b. the treatment is prophylactic treatment of an adult female subject having an expected or established increased risk of GDM,
    c. the treatment is prophylactic treatment of an adult female subject attempting to become or recently pregnant,
    d. the treatment is prophylactic treatment of a foetal subject by administration of the composition or medicament to the foetal subject's mother, or
    e. the treatment is prophylactic treatment of a neonatal, infant or child subject by administration of the composition or medicament to the subject's mother.

12. The use of any one of claims 1-11, wherein
    a. the adult female subject is pregnant,
    b. the adult female subject, or the mother, is 35 years or older,
    c. the adult female subject, or the mother, is pregnant and is 35 years or older,
    d. the adult female subject, or the mother, is pregnant and has a history of GDM,
    e. the adult female subject, or the mother, is pregnant, is 35 years or older, and has a history of GDM,

f. the subject is a foetal subject and the *L. rhamnosus* HN001, or the composition or medicament is to be administered to the subject's mother, or
g. the subject is a neonatal, infant, or child subject, and the *L. rhamnosus* HN001, or the composition or medicament is to be administered to the subject's mother.

13. The use of any one of claims 1-12, wherein the composition or medicament is formulated for simultaneous or sequential administration with a prebiotic.

14. The use of claim 13, wherein the prebiotic comprises fructooligosaccharides, galactooligosaccharides, or human milk oligosaccharides, or a combination thereof.

15. The use of any one of claims 1-14, wherein the adult female subject, or the mother of the foetal, neonatal, infant or child subject, has a BMI of less than 30kg/m^2.