INFORMED CONSENT FORM

1. Study Information

Protocol Title:

The "metabolically-obese normal-weight" phenotype in two Asian ethnic groups and its reversal by calorie restriction and exercise

Principal Investigator & Contact Details:

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Study Sponsor:

Singapore Institute of Clinical Sciences, A*STAR

2. Purpose of the Research Study

You are invited to participate in a research study. It is important to us that you first take time to read through and understand the information provided in this sheet. Nevertheless, before you decide to take part, the research study will be explained to you and you will be given the chance to ask questions. After you are satisfied with your understanding of the study, and decide to take part, you must sign this informed consent form. You will be given a copy of this consent form to take home with you.

You are invited to take part in this study because you are a non-obese person of Chinese or Indian descent, between 21 and 65 years old. During screening, we will briefly evaluate your metabolic health by measuring the levels of glucose (sugar) and insulin (a hormone) in your blood, which provide an indicator of your overall metabolic health, and will allocate you in one of two study groups: metabolically healthy or unhealthy.

This study is carried out to identify the differences in body composition and metabolic function between non-obese people who are metabolically unhealthy and those who are metabolically healthy, and to evaluate the effects of diet and exercise as possible therapeutic approaches to improve metabolic health. A relatively large fraction of the Singaporean population has compromised metabolic health despite not having excess body weight. This is important because these individuals are more likely to go undiagnosed and thus less likely to be treated before clinically overt cardiometabolic disease develops. This study will help identify those subjects and intervene well before metabolic disease ensues.

This study will recruit 80 metabolically unhealthy subjects and 40 metabolically healthy subjects (half Indian and half Chinese) from the National University Health System Hospitals, the Tan Tock Seng Hospital, the National University of Singapore, the Nanyang Technological University, and the general population, over a period of 3 years. Therefore, about 120 subjects will be involved in this study.

3. What procedures will be followed in this study

If you take part in this study, you will undergo a battery of tests to evaluate your body composition and metabolic function at baseline. If you are a metabolically healthy subject, your participation will end at that point. If you are a metabolically unhealthy subject, you will then be randomized to receive one of four interventions: 1) diet-induced mild weight loss (5% of your initial body weight induced by calorie restriction), 2) exercise-induced mild weight loss (5% of your initial body weight induced by endurance exercise), 3) exercise without weight loss, or 4) no change in diet or physical activity. Randomization means that you will be assigned to one of the four groups by chance, like tossing a coin or rolling a dice. You will undergo only one of the four possible interventions, at the end of which the same battery of tests to evaluate your body composition and metabolic function conducted at baseline will be repeated.

If you take part in this study, you will be asked to visit our research centre 4 times at baseline and 4 times after the intervention (if applicable) for testing. These visits will be separated from each other by 4–8 days. During the 1st visit, we will measure your resting metabolic rate, your cardio-respiratory fitness, your body fat content. During the 2nd visit, we will determine the distribution of fat in your body. During the 3rd visit, we will evaluate the sensitivity of your body to the hormone insulin. During the 4th visit, we will measure the ability of your body to handle a mixed meal. During visits 5–8 (if applicable), all testing conducted during visits 1–4 will be repeated.

Your participation in the study will last approximately 1 month if you are a metabolically healthy subject and approximately 6 months if you are a metabolically unhealthy subject. If you are a metabolically healthy subject, your participation will end once you undergo the baseline battery of tests described above. If you are a metabolically unhealthy subject, your participation will consist of the baseline battery of tests described above, followed by a 3-4 month intervention (diet- or exercise- induced mild weight loss, exercise without weight loss, or no change in diet and physical activity), at the end of which the battery of tests described above will be repeated, which will complete your participation in the study. During the 3-4 month intervention, and depending on your group assignment and daily schedule, you will be required to visit our research centre at infrequent intervals to monitor your progress. These visits will be relatively short in duration and less frequent the more compliant you are with the diet and/or exercise prescriptions.

If you agree to take part in this study, the following will happen to you:

Visit 1:

You will arrive in our research centre in the morning, after having fasted overnight. After 30 minutes of rest, a fasting blood sample will be obtained and your resting metabolic rate (i.e. the amount of calories your body needs to maintain your weight while resting) will be measured by using indirect calorimetry, which requires you to breathe for approximately 30 minutes under a clear ventilated hood that allows us to measure the volume and composition of air you inspire and expire.

Your cardiorespiratory fitness (i.e. the maximum amount of oxygen your body can use while exercising) will then be determined during a graded exercise test to exhaustion (on the bike or the treadmill), while you breathe through a mask that allows us to measure the volume and composition of air you inspire and expire. This test will last no longer than 15 minutes.

Finally, your body fat content will be measured by using dual-energy X-ray absorptiometry (DEXA), which is a medical imaging technique that requires you to lie in bed and stay still for approximately 15 minutes while your whole body is scanned.

Visit 2:

You will arrive in our research centre in the morning (there is no need to have fasted for this visit). The distribution of fat in your body and in major metabolic organs such as your liver and muscle will be measured by nuclear magnetic resonance imaging/spectroscopy, which is a medical imaging technique that requires you to lie in a special bed inside a magnet and stay still for a total time of approximately 1 hour (broken down to several shorter intervals) while specific regions of your body (abdomen, muscle, liver) are being scanned.

Visit 3:

You will arrive in our research centre in the morning, after having fasted overnight. The sensitivity of your body to insulin will be evaluated by using a technique called hyper-insulinemic euglycemic clamp, which requires you to lay in bed for approximately 4 hours while we infuse insulin (a major metabolic hormone) and dextrose (a form of sugar) in your body through an intravenous catheter in one arm, and take blood samples from another catheter in the opposite arm (i.e. you will have two intravenous catheters for the duration of this test). At the beginning of this test, you will undergo a muscle biopsy, which involves obtaining a small piece (the size of a corn kernel) of your leg muscle (quadriceps) under sterile conditions and local anesthesia, to evaluate cellular factors involved in sugar handling by your muscle in response to insulin.

Visit 4:

You will arrive in our research centre in the morning, after having fasted overnight. The ability of your body to handle a mixed meal will be evaluated. For this test, you will consume a liquid mixed meal and lie in bed for approximately 3 hours while we obtain frequent blood samples through an intravenous catheter in one arm.

If you are a metabolically healthy person, your participation in the study will end at this point. If you are a metabolically unhealthy person, your participation will continue to a 3-4 month intervention, at the end of which you will conduct 4 additional visits and repeat the tests described above (**Visit 5** will be the same as Visit 1, **Visit 6** will be the same as Visit 2, **Visit 7** will be the same as Visit 3, and **Visit 8** will be the same as Visit 4). These visits will be separated from each other by 4–8 days.

Also, during the intervention, and depending on your group assignment and daily schedule, you will be required to visit our research centre at infrequent intervals to monitor your progress. These visits will be relatively short in duration and less frequent the more compliant you are with the diet and/or exercise prescriptions. In general, however, these visits will be more frequent right before and at the beginning of the intervention (to familiarize you with the diet you will need to consume and/or the exercise you will need to perform) and become less frequent later into the intervention.

In total, the total amount of blood drawn from all research procedures will be ~250 mL (50 teaspoons or 7 tablespoons) at baseline, and another ~250 mL after the interventions (if applicable), over a 4-6 month period.

Any blood and tissue specimens obtained during this study will be stored and analyzed for the purposes of this study for a period not exceeding 10 years upon completion of the study; any unused blood or tissue specimens after this time period will be destroyed. We intend to store your tissue and blood samples beyond the completion of the study as it is likely that results from this study will direct us towards measuring additional metabolites and hormones in your samples. It is also possible that new discoveries in the future may make it feasible to measure new metabolites and hormones relevant to metabolic function, which may require your samples to be sent overseas (outside Singapore). All samples will be de-identified

before storage and analysis, so your personal information will not be disclosed to anybody other than the local research team.

4. Your Responsibilities in This Study

If you agree to participate in this study, you should follow the advice given to you by the study team. You should be prepared to visit our research centre at least 4 times (if you are metabolically healthy) or 8 times (if you are metabolically unhealthy) for periods between 2-5 hours each, and also several shorter visits (if you are metabolically unhealthy), and undergo all the procedures that outlined above.

5. What Is Not Standard Care or is Experimental in This Study

The study is being conducted because diet and exercise are not yet proven to be a standard treatment approach in lean subjects who are metabolically unhealthy. We hope that your participation will help us to determine whether diet and exercise are effective therapeutic approaches for improving metabolic health in lean people with metabolic dysfunction.

Use of a control group (i.e. no change in diet or physical activity) and randomization (study groups assignment by chance) are only done for research purposes and are never part of the standard of care.

Although diet and exercise may be recommended along with the standard of care in some instances, in this study these interventions are only being performed for the purposes of the research, and are not (nor will they be) part of your routine care.

6. Possible Risks and Side Effects

You may experience one or more of the risks indicated below from participating in this study. In addition to these, there may be other unknown risks, or risks that we do not anticipate, associated with participation in this study.

Blood draws and catheter insertion:

Likely / Common:

- Mild discomfort, bleeding, and bruising
- The risk associated with the use of a plastic box to warm your hand up before blood draws (to facilitate blood drawing) may include feeling hot or sweating.

Less Likely / Less Common:

- Occasionally, some people experience dizziness or feel faint during blood drawing and intravenous catheter insertion.

Rare:

- The total amount of blood that will be collected for this research study is ~250 mL (one cup) over 1 month (if you are metabolically healthy), or ~500 mL (2 cups) over 4-6 months (if you are metabolically unhealthy). This includes screening labs and all metabolic tests. This amount is approximately half (250 mL) or as much (500 mL) as you would give during blood donation; the risks associated with giving this amount of blood include headache, nausea, and light-headedness.
- Infection at the site of catheter insertion for blood drawing.
- If the IV catheter slips out of the vein, fluid could collect in your arm and cause swelling and discomfort.
- The use of a plastic box to warm up your hand before blood draws can cause blisters.

DXA (technique for measuring body fat content):

Likely / Common:

- This study involves exposure to radiation from the DXA scan. The amount of radiation from this test, when averaged over the entire body, is equivalent to a

uniform whole-body dose of <1 mrem. This is equivalent to less than 3% of the amount of natural radiation exposure you receive each year. The risk from the radiation exposure in this study is too small to be measured. It is not a big risk when compared with other risks you take every day.

Less Likely / Less Common:

- None.

Rare:

- None.

Magnetic Resonance (MR) scans (techniques for measuring body fat distribution):

Likely / Common:

- None.

Less Likely / Less Common:

- Pain or discomfort from lying still on the MR bed.

Rare:

- Magnetic resonance imaging (MRI) may be harmful for people with metal implants in their bodies, and may cause discomfort in people with a fear of closed spaces. Patients who have certain types of implants will not undergo MRI.

Muscle biopsy:

Likely / Common:

- Possible side effects of the muscle biopsy are mild pain for some time after the procedure. The biopsy site may be tender or sore, causing discomfort, for 2-3 days after muscle biopsy.
- Swelling and/or bruising may occur in the leg on which the muscle biopsy is performed.
- Lidocaine injection for numbing before taking the muscle biopsy may cause local pain or burning sensation upon injection for a few seconds, followed by numbness in the area.

Less Likely / Less Common:

- Muscle biopsy can cause temporary numbness or loss of sensation in the skin in the region of the biopsy site.

Rare:

- Infection at the biopsy site.
- Light headedness, dizziness, pain, nausea may occur during the muscle biopsy.
- Muscle biopsy can cause long-term numbness, loss of sensation or burning pain in the region of the biopsy site.
- Muscle biopsy may be associated with the formation of blood clots.
- Lidocaine injection for numbing before muscle biopsy may cause infection, allergic reaction that may lead to a rash and/or swelling of the injected area.

Metabolic studies: clamp and meal tolerance tests

Likely / Common:

- None.

Less likely / Less Common:

- Some people experience lower back pain or general discomfort from sitting in a chair or lying in bed without being able to stretch for prolonged periods of time (4-5 hours).
- The infusion of insulin during the clamp may cause changes in blood glucose and may cause nausea.
- The liquid mixed meal may taste unfamiliar, or may make you feel nauseous.

Rare:

- Blood glucose levels could change (become low or high) during the infusion of insulin (clamp), which may make you feel nauseated, sweaty, or shaky. However, this risk is extremely small because blood glucose will be carefully monitored throughout the metabolic study.

- Infusion of insulin (clamp) may cause an allergic reaction including rash, swelling of the tongue or throat, and difficulty breathing.

Low-calorie diet consumption:

Likely / Common:

- Weight loss induced by calorie restriction can cause constipation, dehydration, headache and lightheadedness.
- Dietary-weight loss may result in a feeling of weakness.

Less likely / Less Common:

- None.

Rare:

- None.

Exercise:

Likely / Common:

- Exercising at moderate intensity for 30-60 minutes will make you breathe harder, sweat, and may make you feel tired.

Less Likely / Less Common:

- Exercising carries the risk of muscle cramps, muscle soreness, or even accidental injury.

Rare:

- Adverse health changes can occur during exercise including abnormal blood pressure, fainting, disorders of heart rhythm and, in very rare instances, heart attacks or even death.

Confidentiality:

Likely / Common:

- None.

Less likely / Less Common:

- None.

Rare:

- Confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure, and we think the risk of accidental disclosure is very small.

7. Possible Benefits from Participating in the Study

If you participate in this study, you may reasonably expect to benefit in the following ways:

You will receive a detailed health profile at no charge, which will involve your height, weight, body mass index, body fat content, fat distribution, resting blood pressure and heart rate, fasting blood glucose and insulin, resting metabolic rate, and maximal oxygen consumption.

If you are metabolically unhealthy, you may also benefit from the metabolic effects of diet and/or exercise (depending on your group assignment).

Even though there is no assurance you will derive a direct health benefit from participating in this study, your participation may add to our knowledge about the metabolically-obese, normal weight phenotype.

8. Important Information for Women Volunteers

Mild weight loss induced by diet or exercise in a mother may have unfavorable effects on a baby's development. Therefore, pregnant and breast-feeding women may not take part in this study. Women who have a chance of becoming pregnant must have a negative pregnancy test at screening, before participating in the study. If you become pregnant during this study, you should call your doctor and inform the research team immediately.

9. Alternatives to Participation

Participation in this study is completely voluntary. You have the right to stop taking part in the study at any time during the study. If you decide to stop taking part you can be assured you will not be asked for reasons or coerced into continuing against your wishes.

10. Costs & Payments if Participating in the Study

If you take part in this study, the following will be performed at no charge to you: measuring your height, weight, body mass index, body composition (body fat content and fat distribution, blood pressure, heart rate, resting metabolic rate, cardiorespiratory function, and metabolic function tests (insulin sensitivity and pancreatic insulin secretion). These costs will be borne by the Singapore Institute of Clinical Sciences, A*STAR. There will be no costs to you associated with study procedures.

You will be reimbursed for your time, inconvenience and transportation costs as follows:

- If you complete the study, you will be paid $400 if you are metabolically healthy (participation lasting ~1 month; no intervention), or $750 if you are metabolically unhealthy (participation lasting 4-6 months; with diet or exercise intervention).
- If you do not complete the entire study for any reason, you will be paid for each visit you have completed in a prorated manner, as follows: $50 for screening, $100 for the body composition/fat distribution assessment, and $125 for each of the metabolic function tests (clamp and meal).

11. Voluntary Participation

Your participation in this study is voluntary. You may stop participating in this study at any time. Your decision not to take part in this study or to stop your participation will not affect your medical care or any benefits to which you are entitled. If you decide to stop taking part in this study, you should inform a member of the research team. There will not be any consequences to your withdrawal.

However, the data that have been collected until the time of your withdrawal will be kept and analyzed. The reason is to enable a complete and comprehensive evaluation of the study.

The biological samples collected for the study will be deemed to be gifted to the Clinical Nutrition Research Centre / Singapore Institute of Clinical Sciences and will not be returned to you. You will also not have any right or claim to any share in the commercial gain derived from the research (if any). However, you retain your right to ask the Principal Investigator to discard or destroy any remaining samples if they have not been anonymised.

Your doctor, the Investigator and/or the Sponsor of this study may stop your participation in the study at any time if they decide that it is in your best interests. They may also do this if you do not follow instructions required to complete the study adequately. If you have other medical problems or side effects, the study doctor and/or nurse will decide if you may continue in the research study.

In the event of any new information becoming available that may be relevant to your willingness to continue in this study, you (or your legally acceptable representative, if relevant) will be informed in a timely manner by a member of the research team.

12. Compensation for Injury

If you follow the directions of the scientific staff in charge of this study and you are physically injured due to the testing procedures or interventions given under the plan for this study, the Singapore Institute of Clinical Sciences, A*STAR will pay the medical expenses for the treatment of that injury.

Payment for management of the normally expected consequences of your treatment (if applicable) will not be provided by the Singapore Institute of Clinical Sciences, A*STAR.

The Singapore Institute of Clinical Sciences, A*STAR without legal commitment will compensate you for the injuries arising from your participation in the study without you having to prove that the Singapore Institute of Clinical Sciences, A*STAR is at fault. There are, however, conditions and limitations to the extent of compensation provided. You may wish to discuss this with the Principal Investigator.

Compensation for a research-related injury shall be paid by the Singapore Institute of Clinical Sciences, A*STAR according to the Association of the British Pharmaceutical Industry's Clinical Trial Compensation Guidelines. Broadly speaking, the ABPI guidelines recommend that without legal commitment, subjects should be compensated by the Singapore Institute of Clinical Sciences, A*STAR without having to prove that the Singapore Institute of Clinical Sciences, A*STAR is at fault. *There are limitations to compensation in the ABPI guidelines.* A copy of the ABPI guidelines will be provided to you upon request.

By signing this consent form, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence.

13. Confidentiality of Study and Medical Records

Information collected for this study will be kept confidential. Your records, to the extent of the applicable laws and regulations, will not be made publicly available.

However, the Research Institute (SICS), Regulatory Agencies and NHG Domain-Specific Review Board and Ministry of Health will be granted direct access to your original medical records to check study procedures and data, without making any of your information public. By signing this Informed Consent Form, you (*or your legally acceptable representative, if relevant*) are authorizing (i) collection, access to, use and storage of your "Personal Data", and (ii) disclosure to authorised service providers and relevant third parties.

"Personal Data" means data about you which makes you identifiable (i) from such data or (ii) from that data and other information which an organisation has or likely to have access. This includes medical conditions, medications, investigations and treatment history.

Research arising in the future, based on this "Personal Data", will be subject to review by the relevant institutional review board.

Data collected and entered into the Case Report Forms are the property of the Singapore Institute of Clinical Sciences, A*STAR. In the event of any publication regarding this study, your identity will remain confidential.

Any biological samples and/or information containing your "Personal Data" that is collected for the purposes described in this Informed Consent Form will be stored in Singapore. Only anonymised biological samples and/or data will be transferred out of Singapore, if necessary.

By participating in this research study, you are confirming that you have read, understood and consent to the Personal Data Protection Notification available at:

https://www.a-star.edu.sg/sics/Privacy_Policy.aspx.

14. Who To Contact if You Have Questions

If you have questions about this research study, you may contact the Principal Investigator or the Study Coordinator:

Principal Investigator Contact Details:
Assistant Prof. Faidon Magkos
Department of Physiology, Yong Loo Lin School of Medicine, NUS & Singapore Institute for Clinical Sciences (SICS), A*STAR
Brenner Centre for Molecular Medicine (BCMM)
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Study Coordinator Contact Details:
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In case of any injuries during the course of this study, you may contact the Principal Investigator, Assistant Prof. Faidon Magkos; email: faidon_magkos@sics.a-star.edu.sg; tel: +65-6407-0323 (office); +65-8282-9414 (mobile).

The study has been reviewed by the NHG Domain Specific Review Board (the central ethics committee) for ethics approval.

If you want an independent opinion to discuss problems and questions, obtain information and offer inputs on your rights as a research subject, you may contact the NHG Domain Specific Review Board Secretariat at 6471-3266. You can also find more information about participating in clinical research and the NHG Domain Specific Review Board at www.research.nhg.com.sg.

If you have any complaints or feedback about this research study, you may contact the Principal Investigator or the NHG Domain Specific Review Board Secretariat.

CONSENT FORM

Protocol Title:
The "metabolically-obese normal-weight" phenotype in two Asian ethnic groups and its reversal by calorie restriction and exercise

Principal Investigator & Contact Details:
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I voluntarily consent to take part in this research study. I have fully discussed and under-stood the purpose and procedures of this study. This study has been explained to me in a language that I understand. I have been given enough time to ask any questions that I have about the study, and all my questions have been answered to my satisfaction.

By participating in this research study, I confirm that I have read, understood and consent to the Singapore's Institute of Clinical Sciences Personal Data Protection Notification. I also consent to the use of my Personal Data for the purposes of engaging in related research arising the future.

Consent for the Use of Biological Specimen and/or Data for Future Research

☐ Yes, I agree to donate my blood and muscle tissue samples for future research as long as the research is related to metabolic diseases such as diabetes.
☐ No, I do not agree to donate my blood and muscle tissue samples for future research.

_____	_____	_____
Name of Participant	Signature	Date

Impartial Witness Statement
I, the undersigned, certify to the best of my knowledge that the participant signing this informed consent form had the study fully explained in a language understood by him / her and clearly understands the nature, risks and benefits of his / her participation in the study.

_____	_____	_____
Name of Impartial Witness	Signature	Date

Investigator Statement
I, the undersigned, certify that I explained the study to the participant and to the best of my knowledge the participant signing this informed consent form clearly understands the nature, risks and benefits of his / her participation in the study.

_____	_____	_____
Name of Investigator / Person administering consent	Signature	Date