Linking of Omics-based Biomarkers with Nutrition and Metabolic Outcomes in Chinese

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Timely and rigorous peer reviewed
Reputable OA journal over a decade

The main focused on
Integrating nutrition, exercise physiology, clinical investigations, and molecular and cellular biochemistry of metabolism.

Journal scope:
welcomes studies on molecular, cellular and human metabolism

nutritionandmetabolism.biomedcentral.com
Outline

- Background
- Finding from our studies
  - Observational studies
  - Intervention trials
- Currently ongoing studies
Nutrition Transition in China

- **Energy intake from animal foods**

- **Energy intake from fats**

*China National Nutrition Survey (2015)*
Epidemiology of Obesity

- Global: 39% adults with overweight, 12.9% adults with obesity
- China: 34.4% adults with overweight, 6.9% adults with obesity

--- the largest obese population in the world

Prevalence of Type 2 Diabetes in Chinese

1/3 world T2D patients in China

Prevalence of Diabetes in 2012 (%)

113.9 millions

493.4 million
High Susceptibility of Metabolic Diseases in Asians

Multivariate RR of Diabetes among Women with Different Ethnical Backgrounds in the Nurses' Health Study

![Bar chart showing RR for type 2 diabetes among different ethnical backgrounds.]

- White: 1.00
- Asian: 1.99
- Hispanic: 1.73
- Black: 1.38

*Diabetes Care* (2006)

“Metabolic Obesity” in Asians

![Bar chart showing insulin sensitivity in Asians.]

- Insulin Sensitivity: 1.8 mol/min/m², P < 0.001

Few Chinese cohort studies have systematically investigated the roles of genetic and environmental factors for metabolic diseases.
What are nutritional needs and effects of genetic and environmental factors on metabolic risks in Chinese?
Outline

- Background
- Finding from our studies
  - Observational studies
  - Intervention trials
- Currently ongoing studies
To investigate the effect of genetic and environmental factors and their interactions on metabolic diseases.

- **North (Beijing)**
  - Geographic location
  - Genetic factors
  - Differences in disease pattern (e.g., obesity, type 2 diabetes)
  - Exploring risk factors

- **South (Shanghai)**
  - Geographic location
  - Environmental factors
  - Differences in disease pattern (e.g., obesity, type 2 diabetes)
  - Diseases prevention
**Nutrition and Health of Ageing Population in China**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Gene &amp; Environment</th>
<th>Phenotype</th>
<th>Disease</th>
</tr>
</thead>
</table>
| Beijing (n=1600) | Genetic factors  
- GWAS database  
- 2M SNPs  
- 100k CNVs  
- Exome SNPs | Anthropometric Data:  
BP, BMI, waist/hip body composition (DXA)  
Biomarkers:  
- CRP, IL6, TNFR1/2  
- Adiponectin, RBP4, Resistin, PAI-1  
- Glucose, Insulin, lipids, HbA1c  
- Ferritin, vitamin D, vitamin B1  
- Fatty acids profile  
- Amino acids profile  
- Acylcarnitine profile  
- Ionomic profile |  
- Type 2 diabetes  
- Metabolic syndrome  
- Cardiovascular disease  
- Kidney function decline  
- .... |
| Shanghai (n=1600) | Environments  
- Diet  
- Lifestyle  
- Mental health | | |

2005 - 2011
GWAS Database for Obesity and Type 2 Diabetes

Lead National Type 2 Diabetes GWAS in China
- Identified 2 novel (RASGRP1 and GRK5), 23 reported loci for T2D in ~43,000 individuals
- Acquired >0.56M SNPs covering >92% common variants and >1000 common CNVs in Chinese
- Acquired >15M SNPs and CNVs imputed from HapMap and 1000Genome

Lead and joining >10 international GWAS collaborations
- Obesity: 15 novel loci, 62 reported loci
- Height: 17 novel loci, 81 reported loci
- Blood pressure: 27 novel loci, 23 reported loci
- HbA1c: 4 novel loci, 5 reported loci
- Fatty acids: 7 novel loci, 11 reported loci

Genetic Predisposition of Obesity

- \( \uparrow \) Genetic Risk Score (28 BMI-increasing risk loci like \textit{FTO}, \textit{MC4R}, \textit{PCSK1}), \( \uparrow \) BMI, \( \uparrow \) total and trunk fat percentage (DXA)
- \( \uparrow \) Physical activity \( \downarrow \) genetic predisposition for raising BMI

Each additional BMI-increasing risk allele \( \uparrow 7\% \) obesity risk

\[ P \text{ for interaction}=0.022 \]

Genetic Predisposition of Obesity with Diabetes

- Genetic Risk Score (30 BMI-increasing risk loci, like \(FTO,\ MC4R\) and \(PCSK1\)) was associated with ↑T2D
- The association was independent of BMI in Chinese, partly mediated by HOMA-B

\[\begin{align*}
\beta_G &= -0.84 \\ 
(0.15) & \quad P = 1.12 \times 10^{-3} \\
\beta_O &= 0.022 \\ 
(0.005) & \quad P = 0.035 \\
\beta_E &= 0.032 \\ 
(0.13) &
\end{align*}\]

\(\beta_E\) and \(\beta_O\) difference: \(P = 0.969\)

\(P\) value for difference between \(\beta_E\) and \(\beta_O = 0.969\)

\(Diabetologia\) (2014)
Established Erythrocyte Fatty Acid Database

A total of **28** types of fatty acids were detected in **3252** participants

- **Trans FA**
  - 18:1t isomer
  - 18:2n6 9c12t
  - 18:2n6 9t12c

- **PUFA n-6**
  - 18:2n6
  - 18:3n6
  - 20:2n6
  - 20:3n6
  - 20:4n6
  - 22:2n6
  - 22:4n6
  - 22:5n6

- **PUFA n-3**
  - 18:3n3
  - 20:5n3
  - 22:5n3
  - 22:6n3

- **SFA**
  - 14:0
  - 16:0
  - 18:0
  - 20:0
  - 22:0
  - 24:0

- **MUFA**
  - 16:1n9
  - 16:1n7
  - 18:1n9
  - 18:1n7
  - 20:1n9
  - 22:1n9
  - 24:1n9

- Most of cohort studies were from western populations

- Commonly used dietary questionnaires could introduce many measurement errors

- Erythrocyte fatty acids reflect relatively long-term of intakes (essential and trans fatty acids), **particularly important for countries without relevant food composition database like China**

- Evidence regarding the relationships of blood fatty acids with MetS or T2D is limited, and remains controversial
n-3 Fatty Acids and Metabolic Syndrome

Fish Intake are Associated with \( \uparrow \) n-3 FA in Shanghai

Plant Oil Intake are Associated with \( \uparrow \) n-6 FA in Beijing

\( \downarrow \) DHA \( \uparrow \) Number of Metabolic Syndrome Components

\( \text{Erythrocyte membrane DHA proportions} \)
- Total of TFAs are low (0.37% vs 1.8% in US studies)
- Trans-18:1 isomers (≥50% of total TFA) was associated with dairy products

↑ Trans-18:1 was associated with ↓ T2D risk

↑ Trans-18:2 was associated with ↑ dyslipidemia risk

The association between ↑ Trans 18:1 and ↓ 6-yr T2D Incidence was dairy dependent

↑ Dairy intake was associated with ↓ 6-yr T2D Incidence

Carb Intake and De Novo Lipogenesis (DNL)

↑Carb/↓Fat diet

Glucose

Glycolysis

Pyruvate

NADPH

Cytosol

De Novo Lipogenesis

Acetyl-CoA Carboxylase

Fatty Acid Synthase

TCA Cycle

Mitochondria

Elongation

Desaturation

Endoplasmic Reticulum

14:0 → 16:0

16:1n-7 → 18:0

18:1n-7 → 18:1n-9

16:1n-9
↑16:1n-7 was Associated with ↑ MetS Risk and Its Components
DNL Fatty Acids and 6-yr Risks of Metabolic Disease - Cohort

- ↑ DNL fatty acids were associated with ↑ 6-yr incident MetS by 30-51%
- ↑ DNL fatty acids associated with ↑ 6-yr incident T2DM by 20-30%

↑ 16:1n-7, 16:1n-9, and 18:1n-9
↑ 6-yr Incident MetS

↑ 16:0 and 16:1n-7
↑ 6-yr Incident T2DM

Model 1: adjusted for age, sex, region, and residence
Model 2: Model1+ physical activity, education attainment, current smoking and drinking, family history of chronic diseases, total energy intake, carb intake of total energy, and energy-adjusted dietary glycemic index and energy-adjusted glycemic index;
Model 3: Model2+ BMI

Am J Clin Nutr (2013)
Low Carb Intervention Reduced Erythrocyte 16:1n7

Design: A randomized, controlled and parallel trial

Subjects: 50 volunteers (BMI ≥ 24 kg/m²)

Duration: 12 weeks

- Low Carb Group
  Carb: 20-120 g/d

- High Carb + ↓ Calorie Group
  35% calorie restricted
  Carb: 55%; protein: 19%; fat:26%

- Both diets ↓ (~5 kg BW)

- Low carb diet ↑ HDL-C

- Low carb diet ↓ 16:1n7

Unpublished data

16:1n7 was Inhibited in Low Carb Diet

Br J Nutr (2013)
Interaction of Variant in \textit{FADS1} and PUFA on Lipid Profile

\textbf{n-3 Pathway}

\begin{align*}
\text{C18:3 n-3} & \quad \to \\
\text{ALA} & \\
\text{C18:4 n-3} & \\
\text{Δ5desaturase} & \quad (\text{FADS1}) \\
\text{C20:4 n-3} & \\
\text{C20:5 n-3} & \quad \to \\
\text{EPA} & \\
\text{C22:5 n-3} & \\
\text{DPA} & \quad \to \\
\text{C22:6 n-3} & \\
\text{DHA} &
\end{align*}

\textbf{Interaction between} \textit{FADS1-rs174550} \textbf{and} \textbf{18:3n-3 on HDL-C}

\begin{align*}
P \text{ for interaction} & = 0.031
\end{align*}

\textbf{Interaction between} \textit{FADS1-rs174550} \textbf{and} \textbf{18:2n-6 on HDL-C}

\begin{align*}
P \text{ for interaction} & = 0.019
\end{align*}

\textit{J Lipid Res} (2013)
GWAS Meta of PUFA in Chinese and Europeans

Identified 2 Novel Loci (MYB and AGPAT4 for 22:4n-6) in Chinese

Identified 1 Independent Signal (rs2281591) at ELOVL2 for 22:5n-3 in Chinese

Allele Frequency

rs2281591

rs3734398
GWAS Meta of PUFA in Chinese and Europeans

Trans-Ethnic Meta
Identified 2 Additional Novel and Confirmed 5 Loci

**DGAT2**-rs10899123 for 18:3n-6
**PPT2**-rs3134603 for 22:5n-3

Different Effect Sizes of **FADS1** Variants on PUFA Levels between Chinese and Europeans

*Hum Mol Genet* (2016)
GWAS Meta of MUFA in Chinese and Europeans

MUFA Profiles in Chinese and Europeans

16:1n-7

18:1n-7

18:1n-9

20:1n-9

22:1n-9

24:1n-9

Reported Europeans

Europeans

J Lipid Res (2017)
GWAS Meta of MUFA in Chinese and Europeans

Trans-Ethnic Meta found 4 Novel Associations

18:1n-7

PKD2L1

20:1n-9

FADS1

GCKR

J Lipid Res (2017)
GWAS Meta of MUFA in Chinese and Europeans

Trans-Ethnic Meta Confirmed 6 Reported Associations

Manhattan Plot

18:1n-9

FADS1/2

LPCAT3

Effect Size
For 16:1n-7

-0.04
-0.03
-0.02
-0.01
0

FADS1/2
PKD2L1
GCKR
HIF1AN

J Lipid Res (2017)
**GCKR:** Encodes glucokinase (GCK) regulator (GCRP)

rs1260326(C/T, in the 15th exon, p.Pro446Leu)

Glucose \[\xrightarrow{GCK}\] Acetyl-CoA \[\xrightarrow{16:0}\] 16:1n-7

Functional Studies: rs1260326-T \[\xrightarrow{GKRP-Leu}\] ↑GCK activity

Our GWAS: rs1260326-T \[\xrightarrow{16:1n-7}\]

*Hum Mol Genet* 2009

*J Lipid Res* (2017)
**Potential mechanism of SNP at** PKD2L1

**PKD2L1**-rs603424 might influence 16:1n-7 and 18:1n-7 levels by ↓ expression of SCD (Δ9 desaturase)

Adipose Tissue  
Liver  
Skeletal Muscle

rs603424-A ➞ ↓SCD RNA expression (P=10^-6)

J Lipid Res (2017)
Acylcarnitines and Fatty Acid Oxidation

- Acylcarnitines, the intermediates *via* transferring acyl moiety from CoA to L-carnitine
- They transport long-chain (LC) fatty acids to mitochondrial inner membrane
- Hypothesis: ↑ LC-acylcarnitines reflect mitochondria stress and incomplete β-oxidation
A total of 34 free and acylcarnitines were detected in 2,106 participants completed 6-yr follow-up

- Free carnitine and precursor
- Short-chain acylcarnitine
- Medium-chain acylcarnitine
- Long-chain acylcarnitine

Established Acylcarnitines Database

Acylcarnitines \( \uparrow \) Prediction of 6-yr Incident Diabetes

Model 1: conventional model including age, sex, region, residence, smoke, drink, physical activity, family history of diabetes, systolic blood pressure, BMI, glucose & HbA1c, AUC = 0.73;

Model 2: Model 1 + selected acylcarnitines, AUC = 0.90

*Diabetes Care* (2016)
A total of **33** elements were detected in our 6-yr Follow up samples by ICP-MS:

Al, As, B, Ba, Be, Bi, Ca, Cd, Co, Cr, Cu, Fe, K, Li, Mg, Mn, Na, Ni, P, Pb, Se, Sr, V, Zn, S, Mo, Pd, Re, Sb, Si, Sn, Ti and W

↑ **Urinary Nickel Levels were Associated with ↑ T2D Risk**

Adjustment including lifestyle factors, BMI, creatinine, C-reactive protein

*Int J Epidemiol* (2014)
With the publication of the study by Liu et al., nickel appears as a potential new chemical that was missing in our list of environmental chemicals that may be related to diabetes.
What we have found so far?

Genetic Factors
- Found multiple obesity and T2D associated genetic variants
- Different gene structures cannot explain ↑ susceptibility

Environmental Factors
- Diet and nutrient biomarkers
  - DHA, Trans-18:1 (Dairy)
  - Trans-18:2 and DNL fatty acids
  - Ferritin, vitamin D, soy protein
- Lifestyle factors
  - Physical activity
  - Depression
  - Alcohol
- Pollutants

Suggesting potential roles of omics-based biomarkers in determining nutritional status and predicting metabolic diseases
Outline

- Background

- Finding from our studies
  - Observational studies
  - Intervention trials

- Currently ongoing studies
Roles of Vitamin D on Health

- **Bone**: ↑ Remodeling, Maintenance of mineral homeostasis
- **Immune cells**: Improve immunity
- **Adipose**: ↓ pre-adipocyte differentiation
- **Pancreatic β cell**: ↑ Insulin synthesis & secretion
- **Muscle**: ↑ insulin receptor, ↑ glucose uptake
- **Kidney**: ↑ calcium reabsorption, ↓ Renin
- **Parathyroid gland**: ↓ PTH secretion
- **Gut**: ↑ Uptake ingested Ca
Modifying Factors for Vitamin D Status

Environmental factors
- sunlight exposure (season, latitude...)
- dietary intake
- vitamin D supplement
- ...

Physiological factors
- age
- obesity
- skin pigment
- ...

Genetic factors
- GC

Few studies have systematically evaluated effect of genetic and non-genetic factors on vitamin D response
Vitamin D and Metabolic Disorders – Our data

A population-based study (n=3280, aged 50-70 yrs)

**Plasma 25(OH)D Profile**

- **<50 nmol/l**: 6.4%
- **50 ≤25(OH)D <75 nmol/l**: 24.4%
- **≥75 nmol/l**: 69.2%

**↓ 25(OH)D ↑ Metabolic Syndrome**

**↓ 25(OH)D ↑ Insulin Resistance**

**↓ 25(OH)D ↑ 6yr Muscle Mass Loss**

**HOMA-IR**

- BMI <24 kg/m²
- BMI ≥24 kg/m²

**BMI <24 kg/m²**

- Q1: 1.50
- Q2: 1.90
- Q3: 1.90
- Q4: 1.80
- Q5: 1.70

**BMI ≥24 kg/m²**

- Q1: 1.40
- Q2: 1.40
- Q3: 1.50
- Q4: 1.50
- Q5: 1.60

**25(OH)D (nmol/L)**

- Q1 (<41.4 nmol/l)
- Q2 (41.5-56.9 nmol/l)
- Q3 (≥57.0 nmol/l)

**Diabetes Care (2009)**, **J Acad Nutr Diet (2014)**
Vitamin D related Genetic Polymorphisms – Our data

![Diagram showing the relationship between 7-dehydrocholesterol, vitamin D, 25-hydroxylase, and VDBP.]

- **7-dehydrocholesterol** (substrate)
- **Vitamin D**
- **25-hydroxylase**
- **25(OH)D**
- **CYP2R1**
- **VDBP**
- **GC**
- **Cholesterol**

**Graph: 25(OH)D (nmol/l) vs. Number of Risk Alleles**

- **Number of Risk Alleles:** 0, 1, 2, 3, 4, 5+6
- **25(OH)D (nmol/l):** 48, 45, 42, 39, 36, 33

**Statistical Analysis:**

- **P for trend = 4.4 × 10^{-13}**
- **450 IU**
- **11.4 nmol/l**

**References:**

*Human Genetics* (2012)
Randomized Double-blind Placebo-controlled trials

**Trial I**
- 75 Subjects
- 25(OH)D < 50 nmol/l
- VitD<sub>3</sub> doses (IU/d):
  - 0
  - 400 Chinese RDA
  - 800
  - 1200
  - 2000 Chinese UL
- Dose response
- Adverse effect

**Trial II**
- 400 Subjects
- 25(OH)D < 50 nmol/l
- VitD<sub>3</sub> doses (IU/d):
  - 0
  - 2000 IU
- VitD bioavailability
- Effects of genetic factor,
- VitD binding protein
- BMI, sex…
A 3-day food record and information of sunlight exposure and supplement intake were collected every 4 wks.

**Trial I: A Dose–Response Study with VitD₃**

- A 5-arm randomized, placebo-controlled trial
- 20-45 yrs with 25(OH)D <50nmol/l

**Safety assessment**
- Serum calcium ≥ 2.75mmol/L
- Serum 25(OH)D ≥ 220 nmol/L
- Liver and kidney function

**Bioavailability**
- Equilibrium concentration (C)
- Equilibrium time (T)
- The best dosage to maintain 25(OH)D ≥ 50/75 nmol/l

- Placebo (n=15)
- 400 IU/d (n=15)
- 800 IU/d (n=15)
- 1200 IU/d (n=15)
- 2000 IU/d (n=15)

0*# 1* 3* 6* 10* 16*#※

* Blood and urine collection  # physical examination  ※ Questionnaires
Serum 25(OH)D in all the doses (400-2000IU) of VitD₃ reached a plateau at about week 6.
2000 IU/d VitD₃ for 16 weeks ↓80% deficiency without major adverse reactions

Trial I: Efficacy of VitD₃ Intervention
Trial II: Study Design

A double-blind randomized, controlled trial

- 20-40 yrs, 50% men
- 25(OH)D <50nmol/L
- BMI: 18.5-28 kg/m²

A 3-d food record and information of sunlight exposure and supplement intake were collected at week 0, 10 and 20
Trial II: Changes of 25(OH)D Levels

Supplemented 2000IU/d VitD for 20 weeks:

- Net increase of 25(OH)D was $30.6\pm1.7$nmol/L
- There were 25% participants with uncorrected deficiency

![Graph showing serum 25(OH)D levels at week 20 with compliance data and dose effect. The graph includes levels categorized as 25(OH)D < 50nmol/L, 50 ≤ 25(OH)D < 75nmol/L, and ≥ 75nmol/L.]

**Compliance > 95%**
- Yes
- No

**Dose (IU/d)**
- 36.3±9.8nmol/L
- 67.3±23.1nmol/L

**Comparison**
- Placebo: 7.4% (24.6% for 37.7% and 37.7% for 2000IU/d)

*JCEM (2017)*
“Vitamin D Paradox”? African Americans have a lower total serum 25(OH)D but superior bone health.

The New England Journal of Medicine

ORIGINAL ARTICLE

Vitamin D–Binding Protein and Vitamin D Status of Black Americans and White Americans

Community-dwelling black Americans, as compared with whites, had low levels of total 25-hydroxyvitamin D and vitamin D–binding protein, resulting in similar concentrations of estimated bioavailable 25-hydroxyvitamin D. Racial differences in the prevalence of common genetic polymorphisms provide a likely explanation for this observation. (Funded by the National Institute on Aging and others.)

Total 25(OH)D: VDBP-bound (85-90%) + Albumin-bound (10-15%) + Free (< 1%)

Bioavailable 25(OH)D ($25[OH]D_{bio}$)

Cross-sectional studies suggested that associations of $25(OH)D_{bio}$ with serum calcium, PTH or BMD status were stronger than those associations of 25(OH)D.
Ethnic difference in homozygotes distribution

**SNPs in GC produce VDBP variants with different affinities**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
<th>Affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs7041-T (Asp)</td>
<td>Gc1F</td>
<td>$1.12 \times 10^9 \text{ M}^{-1}$</td>
</tr>
<tr>
<td>rs4588-C (Thr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs7041-G (Glu)</td>
<td>Gc1S</td>
<td>$0.60 \times 10^9 \text{ M}^{-1}$</td>
</tr>
<tr>
<td>rs4588-C (Thr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs7041-T (Asp)</td>
<td>Gc2</td>
<td>$0.36 \times 10^9 \text{ M}^{-1}$</td>
</tr>
<tr>
<td>rs4588-A (Lys)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Ethnic difference in homozygotes distribution**

- **Black (N = 658)**
  - GC1S, 5.2% (N = 34)
  - GC2, 2.1% (N = 14)

- **White (N = 367)**
  - GC1S, 76.0% (N = 279)
  - GC2, 18.0% (N = 66)
  - GC1F, 6.0% (N = 22)

- **Chinese (N = 144)**
  - GC1S, 24.3% (N = 41)
  - GC2, 28.5% (N = 41)

- **Gc1F, 47.2% (N = 62)**

Adapted from Powe NEJM (2013), Hum Genet (1993), JCEM (2017)
VDBP Measured by Mono- and Polyclonal ELISAs

- Monoclonal ELISA:
  \[ 165.3 \pm 90.4 \mu g/ml \]

- Polyclonal ELISA:
  \[ 418.7 \pm 99.0 \mu g/ml \ (P < 0.001) \]

The polyclonal ELISA is a prefer method to assess VDBP and 25(OH)D_{bio} for populations with relatively higher Gc1F/1F frequency like Blacks and Chinese.
Vitamin D Metabolism Pathway

Skin

DHCR7

Vitamin D

25-OHase
CYP2R1

25(OH)D

25(OH)D_{Bio}

1α-OHase
CYP27B1

1,25(OH)_{2}D

VDR

24-OHase
CYP24A1

Catabolism

Gene Expression

RXR

GC

Vitamin D binding protein

Diet
Trial II: Gene Variants and 25(OH)D Responses

GC-rs4588 A, CYP2R1-rs10741657 G and VDR-rs2228570 A alleles were associated with ↓ 25(OH)D responses
- Genetic risk score (GRS) = rs4588-A + rs10741657-G + rs2228570-A
- GRS×Treatment interaction (P_{for interaction} = 0.04)

Trial II: GRS×Treatment Interaction and 25(OH)D Responses

![Graph showing the relationship between Genetic Risk Score and 25(OH)D Response]

- 25(OH)D Response (nmol/L)
- Genetic Risk Score
- 13.2nmol/L ~860IU/d

JCEM (2017)
Trial II: BMI and 25(OH)D Responses

BMI per unit → 25(OH)D responses by 1.9nmol/L

$P$ for interaction = 0.009

$\beta = -1.9 \pm 0.4$  
($P < 0.001$)

$\beta = -0.1 \pm 0.2$  
($P=0.51$)
Trial II: Effects of Genetic and Non-genetic Factors

Genetic factors showed stronger impacts than non-genetic factors on $25(\text{OH})D$ and $25(\text{OH})D_{\text{Bio}}$ responses.

Model 1: dose
Model 2: model 1 + non-genetic factors (basal values, gender, BMI)
Model 3: model 1 + genetic factors (genetic risk score)
Model 4: model 2 + model 3

*JCEM* (2017)
Only change of $25(OH)\text{D}_{\text{Bio}}$ was positively associated with change of serum calcium.
Serum PTH level was maximally suppressed when $25(OH)D \geq 50.8$ nmol/L

A potential surrogate for vitamin D deficiency?
Summary

- Daily supplemented 2000 IU VitD₃ ↑ total and bioavailable 25(OH)D levels, but still left uncorrected deficiency
- 25(OH)D_{Bio} might provide additional information reflecting vitamin D physiologic function

When waiting for more studies with bone and cardiovascular outcomes, it is important to take trans-ethnic and interpersonal variations of genetic and non-genetic factors into account for precise vitamin D recommendation and assessment.
Outline

- Background
- Finding from our studies
  - Observational studies
  - Intervention trials
- Currently ongoing studies
Measuring Fatty Acids (N=10,000) from China Kadoorie Biobank Study (n=0.5 million, 10 locations)
Fatty acids and Metabolic Diseases

Characteristics of fatty acids and associations with:
- Obesity (BMI, body fat distribution)
- Muscle distribution and function
- Cardiovascular (BP, ECG, carotid plaque)
- Lung function
- Glucose, HbA1c, HDL-c, LDL-c, TC

Identify fatty acids that are closely associated with diseases.
Genetic and environmental factors contributing to fatty acid levels.
Lay foundation for disease prediction.
Environmental Exposure

↑Unhealthy diet  ↓Physical activity  ↑Stress

- Epigenome
- Transcriptome
- Proteome
- Metabolome
- microbiome

Molecular phenotype

Pathological markers change

Normal ➔ Reversible ➔ Disease

- Precision Nutrition
- Precision Prevention

- Precision Prediction
- Precision Intervention

National Precision Medicine Project for Metabolic Disease

• Obesity
• Diabetes

Therapies:
- Therapy 1
- Therapy 2
- Therapy 3
- Therapy 4
What We Could Do Together?

Ethnic Differences

Gene-Gene

Gene-Environment

Genetic Susceptibility

Gene-Phenotype

Matebolomics

Better Nutrition and Better Health
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Dr. Ling Lu
Dr. Hongyu Wu
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Thanks!
Nickel and Type 2 Diabetes

- **Source**: alloy, electroplating, nickel-cadmium battery, burning coal, fuel oil and waste.
- **Animal studies**: induced hyperglycemia.
- **Human population-based data**: not available