锌-ZnT8 基因多态性与 2 型糖尿病的关联性研究

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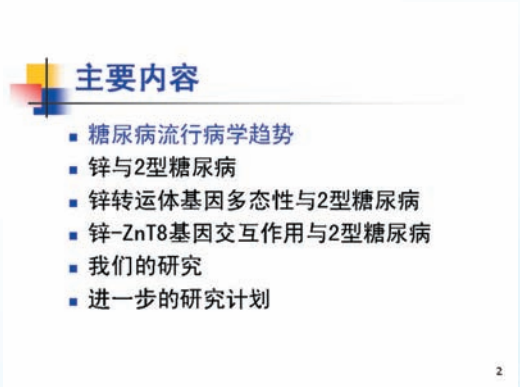

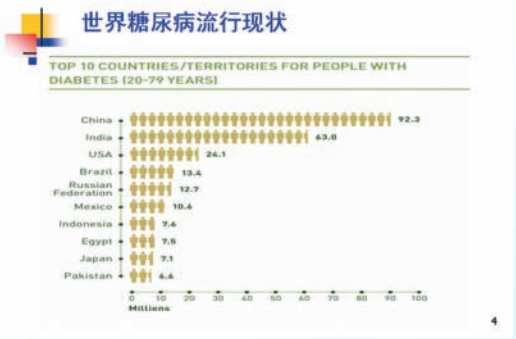

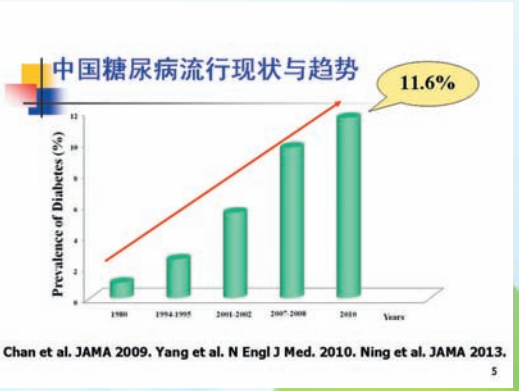

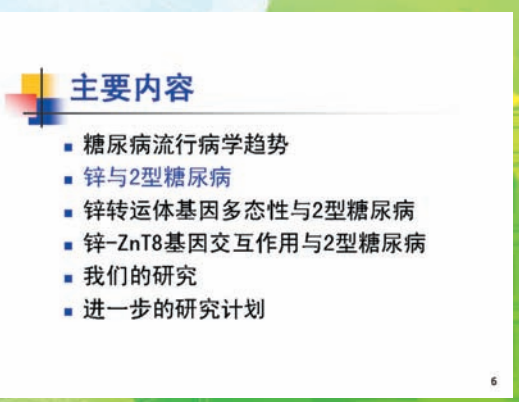

锌与2型糖尿病

锌 —人体必需微量元素

Facilitation within cells	Component of enzymes	Concentration-dependent effects
• Catalytic actions • Structural action • Transcriptional action	• Anti-oxidant enzymes • Enzymes implicated in all processes of insulin	• Peripheral blood mononuclear cells • So on

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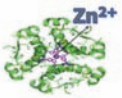
锌与2型糖尿病



70 年前 → 45 年前 ⇨ 40 年前

糖尿病患者胰岛中锌含量较正常人降低50%

胰岛素晶体构成：6个胰岛素分子+2个锌原子

机体锌缺乏会减少高血糖诱导的胰岛素分泌

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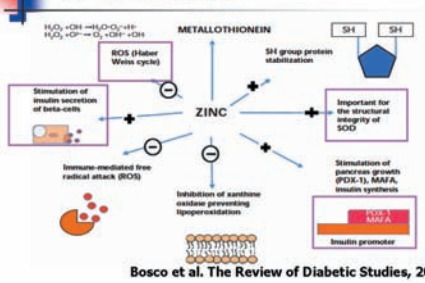
锌与2型糖尿病



Bosco et al. The Review of Diabetic Studies, 2010.7.263

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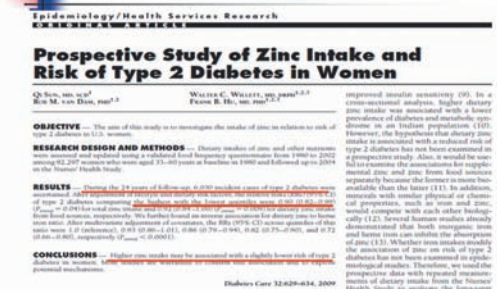
队列研究

高锌摄入可降低糖尿病风险



Epidemiology/Health Services Research
ORIGINAL ARTICLE

Prospective Study of Zinc Intake and Risk of Type 2 Diabetes in Women

Qi Sun, MD, SCD[1] Rob M. van Dam, PHD[1,2] Walter C. Willett, MD, DRPH[1,2,3] Frank B. Hu, MD, PHD[1,2,3]

OBJECTIVE — The aim of this study is to investigate the intake of zinc in relation to risk of type 2 diabetes in U.S. women.

RESEARCH DESIGN AND METHODS — Dietary intakes of zinc and other nutrients were assessed and updated using a validated food-frequency questionnaire from 1980 to 2002 among 82,297 women who were aged 33–60 years at baseline in 1980 and followed up to 2004 in the Nurses' Health Study.

RESULTS — During the 24 years of follow-up, 4,030 incident cases of type 2 diabetes were ascertained. After adjustment of dietary and nondietary risk factors, the relative risks (RRs) of type 2 diabetes comparing the highest quintile with the lowest quintile were 0.80 (0.82–0.99) (P_{trend} = 0.041) for total zinc intake and 0.74 (0.68–0.80) (P_{trend} < 0.0001) for dietary zinc intake from food sources, respectively. We further found an inverse association for dietary zinc to heme iron ratio. After multivariate adjustment of covariates, the RRs (95% CI) across quintiles of this ratio were 1.0 (reference), 0.93 (0.86–1.01), 0.86 (0.79–0.94), 0.82 (0.75–0.90), and 0.72 (0.66–0.80), respectively (P_{trend} < 0.0001).

CONCLUSIONS — Higher zinc intake may be associated with a slightly lower risk of type 2 diabetes in women. Large studies are warranted to examine this association and to explore potential mechanisms.

Diabetes Care 32:629–634, 2009

improved insulin sensitivity (9). In a cross-sectional analysis, higher dietary zinc intake was associated with a lower prevalence of diabetes and metabolic syndrome on an Indian population (10). However, the hypothesis that dietary zinc intake is associated with a reduced risk of type 2 diabetes has not been examined in a prospective study. Also, it would be useful to examine the associations for supplemental zinc and zinc from food sources separately because the former is more bioavailable than the latter (11). In addition, minerals with similar physical or chemical properties, such as iron and zinc, would compete with each other biologically (12). Several human studies already demonstrated that both inorganic iron and heme iron can inhibit the absorption of zinc (13). Whether iron intakes modify the association of zinc on risk of type 2 diabetes has not been examined in epidemiological studies. Therefore, we used the prospective data with repeated measurements of dietary intake from the Nurses'

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队列研究

高锌摄入可降低糖尿病风险

	Quintile of energy-adjusted zinc					
	Q1	Q2	Q3	Q4	Q5	P
Number of women	1785	1784	1784	1784	1784	
Energy-adjusted zinc [median (min, max)]	−1.25 (−4.8, −0.79)	−0.48 (−0.79, −0.23)	0.01 (−0.23, 0.26)	0.50 (0.26, 0.79)	1.24 (0.79, 4.45)	
Number of diabetics	80	60	59	74	60	
Odds ratio						
• Age adjusted	1.00	0.74 (0.53 to 1.05)	0.73 (0.52 to 1.03)	0.99 (0.67 to 1.28)	0.75 (0.53 to 1.05)	0.319
• Age & non-dietary[1] factors adjusted	1.00 1.00	0.82 (0.56 to 1.19)	0.65 (0.44 to 0.96)	0.83 (0.56 to 1.19)	0.56 (0.38 to 0.83)	0.010
• Age, non-dietary[1] and dietary[2] factors adjusted	1.00	0.78 (0.53 to 1.15)	0.60 (0.40 to 0.91)	0.77 (0.52 to 1.13)	0.48 (0.31 to 0.75)	0.004
• Age, non-dietary[1] and dietary[2] factors adjusted plus alcohol intake and use of supplements		0.80 (0.54 to 1.17)	0.60 (0.40 to 0.90)	0.78 (0.53 to 1.15)	0.50 (0.32 to 0.77)	0.006

Vashum et al. BMC Endocrine Disorders，2013

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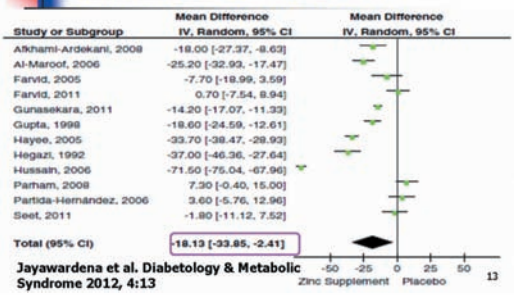
随机对照研究

糖尿病患者补充锌降低血糖水平



Jayawardena et al. Diabetology & Metabolic Syndrome 2012, 4:13

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横断面研究

糖尿病患者锌水平降低

Diabetic Patients VS Controls

Authors	Years	Total Sample No.	Decreased Zinc?
Ferdousi	2012	120	Yes ↓
Basaki	2012	40	Yes ↓
Masood	2009	84	Yes ↓
Aguilar	2007	164	Yes ↓
Maroof	2006	266	Yes ↓
Williams	1995	52	Yes ↓
Islam	2013	280	No →
Zargar	1998	83	No →

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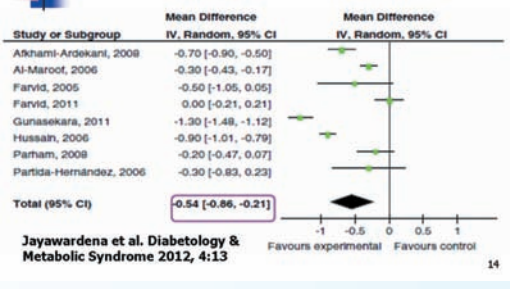
随机对照研究

锌补充降低糖化血红蛋白水平



Jayawardena et al. Diabetology & Metabolic Syndrome 2012, 4:13

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主要内容

- 糖尿病流行病学趋势
- 锌与2型糖尿病
- 锌转运体基因多态性与2型糖尿病
- 锌-ZnT8基因交互作用与2型糖尿病
- 我们的研究
- 进一步的研究计划

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锌转运体与2型糖尿病

二十世纪九十年代中期，锌转运体的发现极大地促进了锌与糖尿病的研究进程

Including ZIP and ZnT families:

- Control the influx and efflux of zinc within cells
- Maintain cellular homeostasis between cell growth and disease prevention

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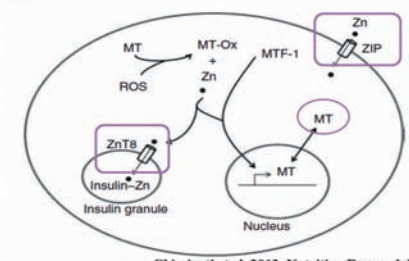
锌转运体与2型糖尿病



Chimienti et al. 2013, Nutrition Research Reviews.

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SLC30A8基因多态性与2型糖尿病

- **SLC30A8: the gene of ZnT8**
- **Including rs13266634 and rs11558471 (Linkage: r = 0.96)**
- **Several genome-wide association studies showed both SNP be associated with type 2 diabetes**

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SLC30A8基因多态性与2型糖尿病

Meta-analysis confirmed the associations

- **SLC30A8 rs13266634 and diabetes**
- **SLC30A8 rs11558471 and diabetes**

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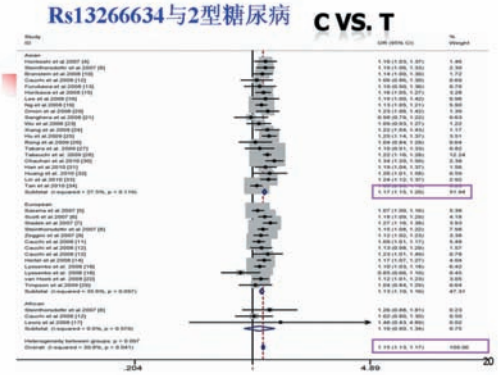
Rs13266634与2型糖尿病 C VS. T



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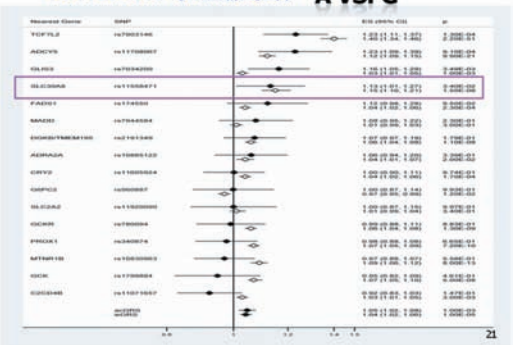
Rs11558471与2型糖尿病 A VS. G



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主要内容

- 糖尿病流行病学趋势
- 锌与2型糖尿病
- 锌转运体基因多态性与2型糖尿病
- 锌-ZnT8基因交互作用与2型糖尿病
- 我们的研究
- 进一步的研究计划

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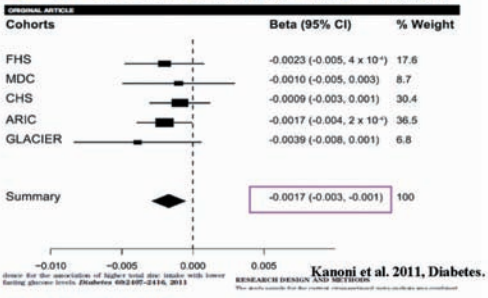
锌- SLC30A8交互作用对血糖水平的影响



Kanoni et al. 2011, Diabetes.

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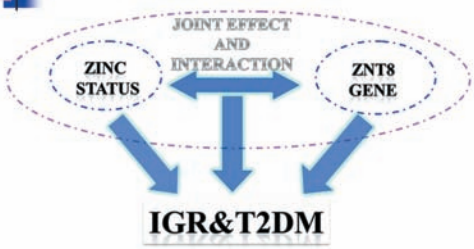
主要内容

- 糖尿病流行病学趋势
- 机体锌水平与2型糖尿病
- 锌转运体基因多态性与2型糖尿病
- 锌-基因交互作用与2型糖尿病
- 我们的研究
- 进一步的研究

研究目的



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研究方法

病例对照研究

- Initiated from December 2004 in Wuhan
- Diagnosed by fasting plasma glucose and oral glucose tolerance test (OGTT)
- Newly-diagnosed type 2 diabetes (T2DM)
- Impaired glucose regulation (IGR)
- Normal glucose tolerance (NGT)

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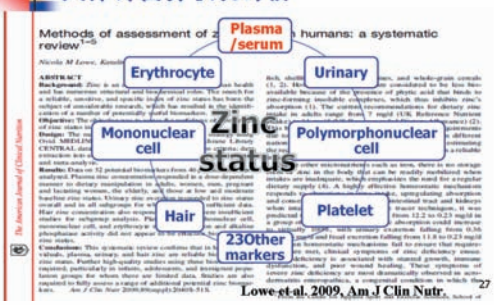
研究方法

人体锌营养状况评价



Lowe et al. 2009, Am J Clin Nutr.

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血浆锌水平的检测

电感耦合等离子体质谱仪(ICP-MS)

ClinChek No. 8883 血浆:
实测：917 ± 67 μg/L
标准: 925 ± 185 μg/L

ClinChek No. 8884 血浆:
实测：1314 ± 114 μg/L
标准: 1363 ± 273 μg/L

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SLC30A8 rs13266634基因分型

Allelic discrimination assay-by-design TaqMan method

ABI7900HT (Applied Biosystems, Foster City, CA, USA)

The genotype success rate: 98.12%

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结果

Anthropometric and metabolic characteristics of 1796 participants.

Parameters	NGT(n=705)	IGR(n=218)	T2D(n=789)	P	P*
Men/women	490/303	121/97	442/343	0.09	0.027
Age (years)	42.48(11.59)	49.68(11.34)	50.98(10.82)	<0.001	<0.001
BMI (kg/m²)	22.95(3.07)	25.53(4.18)	24.97(3.97)	<0.001	<0.001
Family history of diabetes, n (%)	60(7.56)	35(15.06)	111(14.12)	<0.001	<0.001
Hypertention, n (%)	144(18.14)	65(28.02)	263(33.46)	<0.001	<0.001
FPG (mmol/L)	4.56(0.43)	5.98(0.63)	9.82(3.07)	<0.001	<0.001
OGTT2h(mmol/L)	6.44(1.01)	9.13(1.34)	16.49(5.02)	<0.001	<0.001
FPI (# U/mL)	7.07(4.04-9.93)	9.36(6.24-14.22)	8.80(5.44-13.79)	<0.001	0.001
HOMA-beta	88.88(50.63-124.94)	88.93(48.65-125.81)	33.08(15.86-62.50)	0.523	<0.001
HOMA-IR	1.81(0.88-2.76)	2.42(1.61-3.91)	3.68(2.18-5.37)	<0.001	<0.001
TC (mmol/L)	4.34(0.91)	4.55(1.29)	4.79(1.43)	0.018	<0.001
TG (mmol/L)	1.34(1.16)	1.78(1.15)	1.89(1.45)	<0.001	<0.001
HDL-C (mmol/L)	1.34(0.58)	1.41(0.84)	1.43(0.86)	0.307	0.004
LDL-C (mmol/L)	2.69(0.86)	2.51(1.06)	2.59(1.24)	0.054	0.199
Zinc (μg/dl)	161.30(114.56-221.08)	112.96(60.87-145.40)	104.96(65.72-133.69)	<0.001	<0.001

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结果

Associations of plasma zinc concentrations with IGR and T2D

Variables	Tertiles of plasma zinc concentration (μg/dl) 1 (Lowest) < 129.45	2 129.45-197.58	3 (Highest) ≥ 197.58	Per 10 μg/dl of plasma zinc	P value for trend
IGR vs. NGT					
No. of cases/controls	141/265	65/264	12/264		
Crude OR (95% CI)	1	0.46 (0.33-0.65)	0.09 (0.05-0.16)	0.84 (0.83-0.89)	<0.001
Adjusted OR* (95% CI)	1	0.47 (0.32-0.71)	0.10 (0.05-0.21)	0.87 (0.83-0.91)	<0.001
T2D vs. NGT					
No. of cases/controls	559/265	191/264	35/264	/	/
Crude OR (95% CI)	1	0.34 (0.27-0.44)	0.06 (0.04-0.09)	0.85 (0.83-0.87)	<0.001
Adjusted OR* (95% CI)	1	0.36 (0.28-0.48)	0.09 (0.06-0.13)	0.87 (0.85-0.89)	<0.001
(IGR or T2D) vs. NGT					
No. of cases/controls	700/265	256/264	47/264	/	/
Crude OR (95% CI)	1	0.37 (0.29-0.46)	0.07 (0.05-0.10)	0.84 (0.84-0.88)	<0.001
Adjusted OR* (95% CI)	1	0.38 (0.29-0.50)	0.09 (0.06-0.13)	0.88 (0.85-0.90)	<0.001

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结果

Associations of SLC30A8 rs13266634 with IGR and T2D

Genotypes	Tertiles of plasma zinc concentrations 1 (Lowest)	2	3 (Highest)	Per 10 μg/dl of plasma zinc	P value for trend	P value for interaction*
IGR vs. NGT						
TT	1	0.50 (0.20-1.21)	0.06 (0.01-0.47)	0.88 (0.80-0.96)	0.006	
CT	1	0.46 (0.24-0.90)	0.07 (0.02-0.26)	0.87 (0.81-0.93)	< 0.001	0.645
CC	1	0.45 (0.23-0.88)	0.13 (0.04-0.47)	0.86 (0.80-0.92)	< 0.001	
T2D vs. NGT						
TT	1	0.35 (0.20-0.61)	Not estimated*	0.78 (0.72-0.85)	< 0.001	
CT	1	0.32 (0.21-0.50)	0.06 (0.03-0.13)	0.83 (0.80-0.87)	< 0.001	0.01
CC	1	0.40 (0.25-0.64)	0.18 (0.09-0.35)	0.93 (0.90-0.97)	< 0.001	
(IGR or T2D) vs. NGT						
TT	1	0.36 (0.21-0.62)	0.01 (0.001-0.09)	0.81 (0.76-0.87)	< 0.001	
CT	1	0.35 (0.23-0.53)	0.06 (0.03-0.12)	0.84 (0.81-0.88)	< 0.001	0.015
CC	1	0.41 (0.26-0.64)	0.17 (0.09-0.32)	0.93 (0.89-0.96)	< 0.001	

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结果

Interactions between plasma zinc and rs13266634 genotypes

Genotypes	Tertiles of plasma zinc concentrations 1 (Lowest)	2	3 (Highest)	Per 10 μg/dl of plasma zinc	P value for trend	P value for interaction
IGR vs. NGT						
TT	1	0.50 (0.20-1.21)	0.06 (0.01-0.47)	0.88 (0.80-0.96)	0.006	
CT	1	0.46 (0.24-0.90)	0.07 (0.02-0.26)	0.87 (0.81-0.93)	< 0.001	
CC	1	0.45 (0.23-0.88)	0.13 (0.04-0.47)	0.86 (0.80-0.92)	< 0.001	0.645
T2D vs. NGT						
TT	1	0.35 (0.20-0.61)	Not estimated*	0.78 (0.72-0.85)	< 0.001	
CT	1	0.32 (0.21-0.50)	0.06 (0.03-0.13)	0.83 (0.80-0.87)	< 0.001	
CC	1	0.40 (0.25-0.64)	0.18 (0.09-0.35)	0.93 (0.90-0.97)	< 0.001	0.01
(IGR or T2D) vs. NGT						
TT	1	0.36 (0.21-0.62)	0.01 (0.001-0.09)	0.81 (0.76-0.87)	< 0.001	
CT	1	0.35 (0.23-0.53)	0.06 (0.03-0.12)	0.84 (0.81-0.88)	< 0.001	
CC	1	0.41 (0.26-0.64)	0.17 (0.09-0.32)	0.93 (0.89-0.96)	< 0.001	0.015

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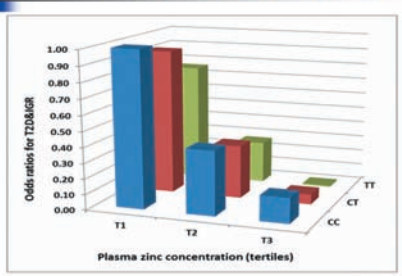
结果

Joint effect of plasma zinc and rs13266634 genotypes



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小结

- 血浆锌浓度与IGR、T2D呈负相关，与对照组相比， IGR、T2D患者血浆锌水平显著降低。
- SLC30A8 rs13266634中的C等位基因携带者患IGR、T2D的风险显著高于T等位基因携带者。
- 血浆锌浓度与SLC30A8 rs13266634之间交互作用显著。与TT基因型携带者相比，CT、CC基因型携带者高浓度血浆锌对T2D的保护作明显降低，但仍具有保护作用。

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Diabetes - Reconsider with Minor ID DB13-0406.R2

Manuscript #: DB13-0406.R2

Title: Interactions between Zinc Transporter-8 Gene (SLC30A8) and Plasma Zinc Concentrations for Impaired Glucose Regulation and Type 2 Diabetes

Dear Dr. Liu:

Your manuscript has been examined by outside reviewers and the editors. We find your data to be of considerable interest, but the reviewers have raised questions that must be addressed. We anticipate that you will be able to respond to each of these and to revise your manuscript accordingly. If the revised manuscript addresses the concerns raised by the reviewers, we expect that it will be accepted for publication in Diabetes. The revision is due 60 days from receipt of this letter.

In addition to the reviewer comments, formatting notes are listed below. Please address these issues when revising your manuscript.

To revise your manuscript, log in to http://mc.manuscriptcentral.com/diabetes and enter your Author Center. Select "Manuscripts with Decisions," locate your prior submission, and click "Create a Revision." Your manuscript number will be appended with an "R" to indicate it is a revision. To reply to reviewers' comments, please select "View Comments and Respond to Reviewers."

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Thank you once again for submitting your work to Diabetes. We look forward to receiving your revised manuscript.

Sincerely,

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Diabetes Journal Editor-in-Chief
American Diabetes Association Editorial Office
5110 Commerce Square Drive Ste. G
Indianapolis, IN 46237

主要内容

- 糖尿病流行病学趋势
- 锌与2型糖尿病
- 锌转运体基因多态性与2型糖尿病
- 基因-环境交互作用与2型糖尿病
- 我们的研究
- 进一步的研究计划

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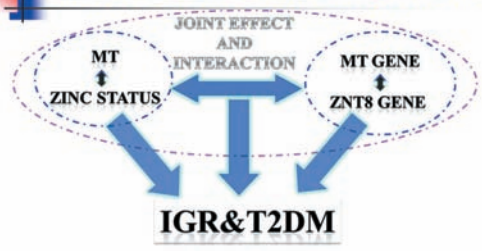
What Are We Planning Now?



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锌补充对2型糖尿病的干预计划

- 400名志愿者招募（已完成）
- 志愿者指标的基线水平测定（已完成）
- 随机双盲对照干预及随访
- 干预指标的分析测定
- 数据的收集分析

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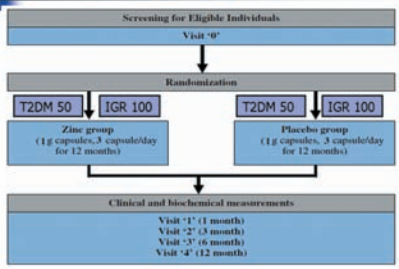
干预技术路线



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个性化干预研究

对志愿者锌转运体基因进行分型，探索不同基因型人群中同一剂量锌补充效果是否存在差异。

如存在差异，后续研究探索不同基因型人群适宜的补充剂量，为之后个性化干预研究提供基础。

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Acknowledgements

- 感谢同济医院、湖北省疾病预防控制中心等单位协助提供研究样本！

2013-12-13

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Acknowledgements

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Thanks for Your Attention !

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