山东大学

硕士学位论文

甲状腺功能正常人群血清TSH水平与血脂的关联性研究

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中文摘要

目的：诸多研究报道显示，不论甲状腺功能正常或者异常，TSH 和血脂都是有一定相关性的。然而，甲状腺激素对于血脂的代谢是有影响的，而且甲状腺激素和促甲状腺激素在体内是有负反馈作用的。本项研究通过回顾性资料分析，探讨甲状腺功能正常的人群，校正甲状腺激素等混杂因素后，TSH 和血脂是否存在相关性。

方法：收集 2004-2009 年于山东省立医院健康查体人群的资料，共 4848 例。排除了甲状腺功能异常人群后，剩余 3664 例人群的资料纳入分析。按照血清 TSH 值的分布将人群分成六组，描述人群的基本情况；通过偏相关系数的计算、一般线性模型、Logistic 回归模型、多元线性回归模型分析 TSH 和血脂的关系；为更准确分析 TSH 和血脂的关系，前三种分析方法中分别建立两种模型，模型一校正性别、年龄、BMI、吸烟史和空腹血糖；模型在模型一的基础上增加校正甲状腺激素。

结果：1. 我们得到六个组性别、吸烟状态、年龄 、FPG、HDL-C、FT3、FT4、TT3 和 TT4 的差异是有统计学意义的。2. 偏相关分析、一般线性模型和多元线性回归模型分析显示，校正所有混杂因素后，TSH 和 logTC 的 r=0.049（P=0.004），线性变化系数为 0.017（p=0.021），偏回归系数为 0.003（P=0.006）。分年龄组进行偏相关分析，结果显示在 50 岁之前，两者关系变化不明显，但是当年龄大于 50 岁后，随着年龄的增大，TSH 与总胆固醇的偏相关系数增加趋势明显。3. 校正所有混杂因素后，在偏相关分析中，TSH 和 log 转换后的 LDL-C、HDL-C 以及 TG 的偏相关系数分别为 0.049（P= 0.005），-0.004（P=0.818），0.059（P=0.000）；一般线性模型分析中 TSH 和 log 转换后的 LDL-C、HDL-C 以及 TG 的线性系数分别为：0.011(p=0.281), -0.006（p=0.529），0.074（p=0.001），趋势和偏相关分析是一致的；在多元线性回归分析中，TSH 和 log 转换后的 LDL-C 以及 TG 的偏回归系数分别为 0.005(P=0.008)，0.013（P=0.001）4. 六个组的高胆固醇血症的患病率随着血清 TSH 升高有增高的趋势，只是尚无统计学意义（P=0.322）。在 logistic 回归模型中，将性别、年龄、BMI、吸烟史和血糖作为混杂因素校正后，得到 TSH 第二组到第六组与第一组比较的优势比（OR）分别为 1.824、2.037、1.925、

2.105 和 3.239；在上述模型的基础上再校正了甲状腺激素后，优势比分别为1.803、2.012、1.909、2.104、3.194，比未校正甲状腺激素时优势均有所降低，但是总体趋势不变。

结论：通过对3664例甲状腺功能正常人群的血脂分析，发现正常参考范围的TSH和血脂有一定的相关性，而且年龄增高时，这种相关性更加明显。具体来说，通过偏相关分析，一般线性模型，多元线性回归模型和Logistic回归模型分析，我们发现TSH和总胆固醇、低密度脂蛋白、甘油三酯以及高胆固醇血症患病的危险度是有正相关性的，而且在校正了甲状腺激素的作用后，这种相关性依然存在。

关键词：TSH，甲状腺功能正常人群，血脂，总胆固醇，相关性，回顾性研究

Abstract

Objective: Thyroid function and TSH is associated with the level of serum lipid. And serum choleaterol may be associated with TSH even if the TSH is narrowed within the reference range.As we know, thyroid hormones are negatively associated with TSH, in our retrospection research, we focus on the association of serum lipid and TSH within the reference range after adjustment of thyroid hormones.

Materials and Methods: We retrospectively reviewed 4848 subjects who were self-referred for a rountine health check-up at Provincial Hospital affiliated to Shandong University from January 2004 to December 2009. We exclude the persons in non-euthyroid status and those using thyroid medication to gain the euthyroid population. Finally, 3664 euthyroid general population were evaluated.,they were divided in six groups according to serum TSH levels. Relations between TSH levels and lipids were analyzed by partial correlation analyses, general linear analysis, multivariate logistic regression analysis and multiple linear regression analysis.2 models were constructed in order to compare and adjust the effect of thyroid hormones: Model 1 was adjusted for gender,age, smoking status, BMI and FPG; Model 2 added thyroid hormones besides the factors in model 1.

Result: 1. There were significant differences in the composition of gender、smoking status and means of age、FPG、HDL-C、FT3、FT4、TT3、TT4 across the six groups, while other parameters had no statistically significant difference. **2.** After all confounding factors considered,the the linear coefficient was 0.017 (P=0.021), and the partial regression coefficient was 0.003 between logTC and TSH. Then we divided the population into 6 subgroups according to age, the relationship between TSH and TC was notobvious if the persons were younger than 50 years old, but the relationship became distinct in the elder population. **3.** In partial correlation analysis(model 2), the partial correlation coefficients between TSH and the log transform of LDL-C,HDL-C and TG were 0.049（P= 0.005），

-0.004（P=0.818），0.059（P=0.000）. In general linear analysis,the linear coefficient were 0.011(p=0.281), -0.006 （ p=0.529 ） and 0.074 （ p=0.001 ） respectively(table3),which was consist with the partial correlation analysis. In multiple linear regression analysis, TSH was positive with LDL-C and TG, whose regression coefficients were 0.005(P=0.008) and 0.013 （ P=0.001 ） .4. The prevelance of hypercholesteremia in the 6 groups were showed a rising trend, but the difference made no statistically sense(P=0.322).

Conclusion: In this study, we explore the relationship between TSH and serum lipid through the data from 3664 euthyroid subjects. We found there were positive associations between TSH and TC、 LDL-C 、 LDL-C 、 TG 、 hypercholesteremia. Moreover, the relationship still remained the same after thyroid hormones adjusted. Beyond those results, we also discovered that TC showed a negative relationship with thyroid hormones in the multiple linear regression analysis. Finally, our data showed that TSH within the reference range was related with components of lipids. Besides, the correlation was stronger when the age became elder. This study is, to our knowledge, the first that addresses the possible linkage between TSH within reference range and serum lipids after the adjustment of thyroid hormones.

Key words: TSH，euthyroid population，serum lipid，TC，ralatinship study，retrospective study

符号说明

符号	英文名称	中文名称
BMI	body mass index	体重指数
CI	confidence interval	可信区间
FPG	fasting plasma glucose	空腹血糖
FT3	free triiodothyronine	游离三碘甲状腺原氨酸
FT4	free thyroxine	游离甲状腺激素腺
HDL-C	high density lipoprotein-cholesterol	高密度脂蛋白胆固醇
HMGCR	HMG CoA reductase	HMG 辅酶 A 还原酶
LDL-C	low density lipoprotein-cholesterol	低密度脂蛋白胆固醇
Log(**)	logarithmical（**）	对数转换后的（**）
OR	odds ratio	比值比
SPSS	Statistical Package for the Social Sciences	社会科学的统计软件包
TC	total cholesterol	总胆固醇
TG	triglyceride	甘油三酯
TSH	thyroid stimulating hormone	促甲状腺激素
TT3	total triiodothyronin	总三碘甲状腺原氨酸
TT4	total thyroxine	总甲状腺激素

前言

甲状腺激素是体内重要的激素之一，对能量物质代谢以及生长发育发挥重要的生理，其主要通过 2 个途径发挥其生理作用：①作用于细胞膜上 Na-K-ATP 酶，促进细胞内 ATP 生产 ADP 增多，促进线粒体的吸收，增加耗氧和产热，继而调节细胞的能量代谢和物质代谢.②与核受体结合，调节细胞内 DNA、RNA 以及蛋白质的合成与代谢。这两条途径都参与了对脂类代谢的调节。

甲状腺功能和血脂的代谢密切相关，甲状腺功能减退时，血清总胆固醇、低密度脂蛋白、甘油三酯会增高，患冠心病的风险会增加[1-3]；近来研究发现，亚临床甲减时，很多报道显示血清总胆固醇和低密度脂蛋白胆固醇会有不同程度的增高[1-9]，而高密度脂蛋白会有不一致的变化[8-17]。当甲状腺功能发生异常时，人体的血脂谱通常会发生改变。以往的研究发现，甲状腺功能低下的病人会出现血清总胆固醇，LDL-C 水平增高。甲亢病人血脂的变化与甲减病人通常是相反的。血清总胆固醇，LDL, HDL，apoB 有降低的趋势。亚临床甲状腺功能低下是指病人的血清 TSH 水平增高，但是血清甲状腺激素水平正常，而且没有临床甲状腺功能低下的症状。关于这一类人群血脂的变化研究报道也很多，Tromso 等研究发现亚甲减组的病人血清 LDL-C 明显高于对照组，ApoA1 明显低于对照组；女性患者的血清总胆固醇水平也明显增高，随后的甲状腺激素干预实验发现，当 TSH 水平维持在 0.2-2.0 m IU/L 时，TC, LDL-C, ApoB 水平都会降低。当 TSH 在正常范围内变化时，相应的血脂变化也有一些研究和报道。最近很多研究将 TSH 的范围缩窄到正常参考范围，此时的胆固醇也会随着 TSH 在正常范围的增高而呈现一定的变化[18-22, 23-29]。两个小规模的人群研究显示，当 TSH 在正常参考范围内增高时，血清总胆固醇和 LDL-C 增高，HDL-C 则呈现相反的变化趋势。而且给 TSH 位于正常范围高值的人群以甲状腺素治疗时，血清总胆固醇和 LDL-C 降低。随后 HUNT 的大范围的人群研究也有类似的发现。通过上面的阐述我们发现，很多情况下不论甲状腺激素的水平是否正常，胆固醇的变化都是和 TSH 一致的，通常来说，胆固醇都是随着 TSH 的升高而呈现增高的趋势。

既往的关于 TSH 在正常范围时和血脂关系的研究，都没有考虑甲状腺激

素对胆固醇等混杂作用，然而，甲状腺激素和TSH在人体内是存在负反馈作用的[30]，而且有一些文献报道甲状腺功能正常时，甲状腺激素和血脂是有相关性的[21, 23, 24, 30, 31, 32]，所以甲状腺激素是影响我们研究TSH和血脂关系的混杂因素。因此，我们想通过此次回顾性研究来探讨甲状腺功能正常人群，随着TSH在正常范围增加时，血清胆固醇的变化趋势，并证明这种变化是不依赖甲状腺激素的作用的

材料和方法

1. 研究设计：

以健康查体人群作为研究对象，收集性别、年龄、身高、体重、吸烟史、家族史等基本资料，以及甲状腺功能和血脂等血清学指标检测结果。

2. 研究现场：

我们从山东省立医院查体中心收集到了 2004-2009 年部分查体人群的资料。所有入选人群均填写一份设计调查表。

3. 研究对象：

纳入标准：所有入选人群必须有甲状腺功能和血脂的血清学检测指标，并具个人基本资料。

排除标准：(1) 患有冠心病以外的其他心脏病、甲状腺肿大、有甲状腺疾病个人史和家族史者；(2) 患有下丘脑垂体疾病、糖尿病及其它内分泌疾病、恶性肿瘤、急性脑血管病、严重的肝肾疾病、遗传性高脂血症者；(3) 近 3 个月曾服用调脂药物或影响甲状腺功能的药物者(如胺碘酮等含碘药物、锂剂、a-干扰素、苯妥英钠、多巴胺及激素等)；(4) 妊娠或哺乳妇女。

甲状腺功能正常的定义主要依据血清学检测指标 TSH、FT3、FT3、TT3 和 TT4 甲状腺功能异常的诊断，参考《中国甲状腺疾病诊治指南》的实验室检查标准：(1) 甲状腺功能亢进症：TSH 低于正常参考值，FT3 和(或)FT4 高于正常参考值。(2) 亚临床甲亢：TSH 低于正常参考值，FT3 、FT4 正常。(3) 甲状腺功能减退症：TSH 高于正常参考值，FT3 和(或)FT4 低于正常参考值。(4) 亚临床甲减：TSH 高于正常参考值，FT3 、FT4 正常。

血脂异常的诊断标准按《中国成人血脂异常防治指南》规定的标准，高胆固醇血症：TC > 6.2mmol/L。

4. 研究变量：

人群的基本信息：性别，年龄，身高，体重（BMI），吸烟史；

血清学指标（空腹血，当天测量）：血糖，血脂（总胆固醇、高密度脂蛋白、低密度脂蛋白、甘油三酯），甲状腺功能指标（促甲状腺激素、游离三碘甲状腺原氨酸、游离甲状腺素、三碘甲状腺原氨酸、甲状腺素）

5. 测量：

进行流行病学研究的人群均完成一份问卷，获得他们的性别，年龄，吸烟史等信息；查体中心的人群，通过查体中心的工作人员参与基本信息的完善。身高、体重的测量均由我院经过正规培训的护士进行测量，每一天的测量固定一位护士进行，以减少因为人因素造成的误差。BMI=体重（kg）/身高（m）^{2}

血清学指标的测量均于山东省立医院的检验科进行：血糖和血脂是由OLYMPUS AU5400 生化仪以及其配套试剂盒测量的，参考范围分别是：血糖3.9-6.3 mmmol/L；总胆固醇 3.6-6.2 mmol/L；高密度脂蛋白 0.8-1.5 mmol/L；低密度脂蛋白 0.5-3.36 mmol/L；甘油三酯 0.4-1.8 mmol/L；

甲状腺功能的测量采用西门子 ADVI centaur XP 系统及其配套试剂盒，参考范围分别是：促甲状腺激素（TSH） 0.35-5.5 m IU/L；游离三碘甲状腺原氨酸（FT3）3.5-6.5 pmol/L；游离甲状腺素（FT4）11.5-22.7 pmol/L；三碘甲状腺原氨酸（TT3）0.92-2.79 ng/mL；甲状腺素(TT4) 58.1-140.6 ng/mL；

6. 偏倚：

在研究 TSH 和血脂的关系时，将其他因素包括性别、年龄、BMI、吸烟史、空腹血糖和甲状腺激素等均作为混杂因素进行校正。

7. 样本大小：

合计 4848 例，按照排除标准筛选后，最终甲状腺功能正常的人群有 3709 例。将所有研究对象进行单因素两变量回归分析，剔除剩余标准差绝对值大于 3 的数据 45 例，最终进入分析的数据合计 3664 例。

8. 统计学方法：

一、由于 FT3、FT4、TT3 和 TT4 之间存在共线性，为了校正甲状腺激素的作用，我们提取了三个主成分（方差贡献率为 87.729%）[33]，分别如下：

$$\text{Factor1} = 0.192\times\frac{FT_3-4.9869}{0.65884}+0.392\times\frac{FT_4-17.4741}{2.66429}+0.464\times\frac{TT_3-1.3610}{0.45369}+0.468\times\frac{TT_4-98.3905}{25.94527}$$

$$\text{Factor2} = 0.701\times\frac{FT_3-4.9869}{0.65884}+0.402\times\frac{FT_4-17.4741}{2.66429}-0.253\times\frac{TT_3-1.3610}{0.45369}-0.375\times\frac{TT_4-98.3905}{25.94527}$$

$$\text{Factor3}=0.552\times\frac{FT_3-4.9869}{0.65884}-0.766\times\frac{FT_4-17.4741}{2.66429}+0.641\times\frac{TT_3-1.3610}{0.45369}-0.221\times\frac{TT_4-98.3905}{25.94527}$$

关于三个主成分的解释：

第一个综合反映甲状腺激素的四个指标；

第二个反映的是FT3和FT4；

第三个反映的FT3和TT3。

二、首先将TSH按照百分位数分布（2.5,26.25,50,73.75,97.5）分成6组[35]：0.27 m IU/L≤TSH<0.62 m IU/L为一组；0.62 m IU/L≤TSH<1.36 m IU/L为二组；1.36 m IU/L≤TSH<1.93 m IU/L为三组；1.93 m IU/L≤TSH<2.66 m IU/L为四组；2.66 m IU/L≤TSH<4.61 m IU/L为五组；4.62 m IU/L≤TSH≤5.50 m IU/L为六组；然后按照TSH将人群分成六个亚组，对人群的基本资料描述，连续型变量通过均数±标准差进行描述，分类变量以构成比的形式进行描述，并比较各亚组间的差别。

三、通过一般线性模型、多元线性回归模型、Logistic回归模型和偏相关系数的计算来分析TSH和胆固醇的关系：

①偏相关系数的计算：校正其他混杂因素后，计算TSH和总胆固醇、高、低密度脂蛋白胆固醇和甘油三酯的偏相关系数，校正甲状腺激素前后比较系数的变化。

②一般线性模型：由于总胆固醇、高、低密度脂蛋白胆固醇和甘油三酯均不服从正态分布，进行log正态转换后分析。将性别、年龄、BMI、血糖、吸烟史、TSH作为分组变量，甲状腺激素作为协变量，分别统计按照TSH分成六组后比较六组间的总胆固醇、高、低密度脂蛋白胆固醇和甘油三酯的差别有没有统计学意义以及它们与TSH之间的线性系数。

③多元线性回归模型：将性别、吸烟史作为分组变量，将年龄、BMI、血糖、TSH、甲状腺激素作为连续型变量，以P=0.05为进入模型的标准，P=0.10为出模型的标准进行逐步回归分析，总胆固醇、高、低密度脂蛋白胆固醇和甘油三酯进行log转换后作为因变量统计其与TSH的偏回归系数。

④Logistic回归模型：将高胆固醇血症患病与否作为因变量，将性别、吸烟史作为分组变量，将年龄、BMI、血糖、TSH、甲状腺激素作为连续型变量，

以 P=0.15 为进入模型的标准，P=0.15 为出模型的标准进行逐步回归分析，计算按照 TSH 分组的各组与第一组比较患高胆固醇血症的优势比，并进行甲状腺激素校正前后的比较。

通过偏相关系数的计算、一般线性模型、Logistic 回归模型、多元线性回归模型来分析 TSH 和胆固醇的关系（有统计学意义指 *P* 值小于 0.05）：在前三种分析方法中分别建立两种模型，模型一是指校正性别、年龄、BMI、吸烟史和空腹血糖；模型二是指在模型一的基础上在再多校正甲状腺激素。多元线性回归模型中以 P=0.05 为进入模型的标准，P=0.10 为出模型的标准进行逐步回归分析；Logistic 回归模型中以 P=0.15 为进入模型的标准，P=0.15 为出模型的标准进行逐步回归分析，计算按照 TSH 分组的各组与第一组比较患高胆固醇血症的优势比。上述统计学分析均是通过 SPSS17.0 软件完成的。

9. 我们此次研究经医院伦理委员会批准，所有人都签署知情同意书

结果

1. 总体资料的描述（表格一）

共收集了 4848 例人群的基本资料，排除甲状腺功能异常以及单因素两变量回归分析剩余标准差绝对值大于 3 的人群后，最终 3664 例纳入研究分析。我们将这 3664 例人群按照 TSH 分成六组后，分别描述六个组的人群的基本情况，通过对六个组以上各项基本指标的总体比较，我们得到六个组性别、吸烟状态、年龄 、FPG、HDL-C、FT3、FT4、TT3 和 TT4 的差异是有统计学意义的，其他几个变量的变化尚不具有统计学意义。六个组的性别、吸烟史、FPG、甲状腺激素等的不均衡，提示本研究进行混杂因素（包括甲状腺激素）校正的必要。

2. 偏相关分析（表格二）

在偏相关分析中，将性别、年龄、吸烟史、BMI 和血糖作为混杂因素校正后，总胆固醇、高、低密度脂蛋白胆固醇和甘油三酯进行 log 正态转换后得到它们与 TSH 的偏相关系数分别为 0.045、0.001、0.044、和 0.058，除高密度脂蛋白外均有统计学意义；在上面校正的混杂因素的基础上，再校正甲状腺激素后得到的偏相关系数没有明显变化，主要是高密度脂蛋白胆固醇的偏相关系数变为负数-0.004，尚不具有有统计学意义，其他三个的系数分别为 0.049、0.049 和 0.059，均有统计学意义。

从统计学结果可以看出，TSH 和总胆固醇、甘油三酯、低密度脂蛋白之间是存在正相关的，即随着 TSH 的增高，总胆固醇、甘油三酯和低密度脂蛋白有增高的趋势，且这种趋势是不依赖甲状腺激素的作用的。TSH 和高密度脂蛋白之间的关系校正甲状腺激素之前为正相关，校正之后为负相关，均没有统计学意义，提示甲状腺激素和 TSH 对于胆固醇的作用是相反的，校正甲状腺激素才可以准确的探讨 TSH 对胆固醇的影响。

3. 一般线性模型（表格三）

两个模型中 TC、HDL-C、LDL-C 和 TG 的几何均数绘成折线图，见图 1-4。可见模型一与模型二的差别不是很大，最终校正所有混杂因素的模型二中，TSH 分成六组与 log TC、logHDL-C、logLDL-C 和 logTG 的线性系数（P 值）分别

是 0.017（0.021）、-0.006（0.529）、0.011（0.281）、0.074（0.001）。在模型二中，组间两两比较可以发现，对于总胆固醇来说，第二至五组和第一组比较差别均有统计学意义，第二组和第四组比较差别也有统计学意义；对甘油三酯来说，第一组和第 4、5、6 组比较，第二、三、四组和第六组比较差别也有统计学意义；对于低密度脂蛋白胆固醇来说，第一、二组和第四组之间的差别有统计学意义；对于高密度脂蛋白胆固醇来说，任意两组间比较都没有统计学意义。（上述结果未列出）

从统计结果可以看出，总胆固醇、低密度脂蛋白胆固醇和甘油三酯均有随着 TSH 的增加逐渐增高的趋势，对于 TC 和 TG 而言，这种趋势有统计学意义；而高密度脂蛋白胆固醇有降低的趋势，而且线性系数很小，仅为 0.006，尚不具有统计学意义；对于总胆固醇和低密度脂蛋白胆固醇而言这种增高的趋势不是连续存在的，对于 TC 而言，当 TSH >2.65 m IU/l 时这种趋势反而降低，对于 LDL-C 而言，当 TSH>4.60 m IU/l 时这种增高的趋势反而略有降低。

4. 多元线性回归模型（表格四）

从表格四可以看出，对于总胆固醇、低密度脂蛋白胆固醇和甘油三酯而言，所有变量均能纳入多元线性回归模型，对于高密度脂蛋白胆固醇来说，只有性别、BMI 和甲状腺激素能够进入模型。TSH 和总胆固醇、低密度脂蛋白胆固醇、甘油三酯的偏回归系数分别为 0.003, 0.005 和 0.013，均有统计学意义，即 P<0.05. 校正后的偏回归系数大小比较：对于总胆固醇而言，年龄>性别>血糖>吸烟史>BMI>甲状腺激素>TSH；对于低密度脂蛋白而言，年龄>BMI>血糖>吸烟史>性别>TSH>甲状腺激素；对于甘油三酯而言，BMI > 血糖>年龄 >性别> TSH >甲状腺激素；对于高密度脂蛋白胆固醇而言，性别>BMI >甲状腺激素。

从统计结果可以看出，TSH 对于总胆固醇、甘油三酯和低密度脂蛋白的变化是有影响的，但是在所有的考虑因素之中 TSH 均是影响效果比较小的变量，偏回归系数分别是 0.003, 0.013 和 0.005.，即 TSH 每增高 1 m IU/L，总胆固醇、甘油三酯、低密度脂蛋白分别增加 1.006 mmol/L, 1.030 mmol/L 和 1.012 mmol/L.

对于高密度脂蛋白胆固醇而言，TSH 和它的关系尚不明确。甲状腺激素和总胆固醇是负相关的，与甘油三酯是正相关的，与低密度脂蛋白胆固醇最终的

综合效应也正相关的。

5. 多元 logistic 回归分析（表格五）

通过对 TSH 六分组的各组的高胆固醇血症患病率的计算得到六个组的患病率分别是：10.71%、15.54%、16.13%、14.71%、16.24%和 22.67%，绘成折线图见图五，从折线图可见随着 TSH 分组，患病率有逐渐增高的趋势，总体比较各组患病率没有统计学意义，*P*值为 0.322。组间两两比较发现第一组和第六组之间的患病率差别有统计学意义，*P*=0.027。在 logistic 回归模型中，将性别、年龄、BMI、吸烟史和血糖作为混杂因素校正后，得到 TSH 第二组到第六组与第一组比较的优势比(OR)分别为 1.824、2.037、1.925、2.105 和 3.239；在上述模型的基础上再校正了甲状腺激素后，优势比分别为 1.803、2.012、1.909、2.104、3.194，比未校正甲状腺激素时优势比有所降低，但是变化不大，详见表五。

从上述统计结果可以看出，随着 TSH 的增加，高胆固醇血症的患病率的危险度总体上有逐渐增高的趋势，虽然第四组较第三组有所降低，而且这种趋势在校正了甲状腺素激素的作用后依然存在。

综上所述，通过偏相关分析，一般线性模型，多元线性回归模型，logistic 回归分析，我们发现 TSH 和总胆固醇、低密度脂蛋白、甘油三酯是有正相关性的，而且在校正了甲状腺激素的作用后，这种相关性依然存在。校正了其他混杂因素后，正常范围的 TSH 和 logTC 的一般线性系数、偏相关系数、偏回归系数分别是 0.017、0.045、0.003；TSH 和 logTG 的一般线性系数、偏相关系数、偏回归系数分别是 0.074、0.058、0.013；TSH 和 logLDL-C 的一般线性系数、偏相关系数、偏回归系数分别是 0.011、0.044、0.005；TSH 和 logHDL-C 的一般线性系数和偏相关系数均为负值，但是尚不具有统计学意义；在多元线性回归模型中，我们发现甲状腺激素和总胆固醇、高密度脂蛋白胆固醇是负相关的，和低密度脂蛋白以及甘油三酯是正相关的。

在一般线性模型中，通过组间两两比较发现，总胆固醇、低密度脂蛋白均数最高值均位于第四组，它和均数比较低的第一组和第二组比较是有统计学差异的；对于甘油三酯而言，这种随着 TSH 增高的趋势是连续的，第六组和第一到四组比较均是有统计学差异的；

在 logistic 回归模型中，校正甲状腺激素前后，后五个组与第一组比较的 OR 值差别不大，都是随着 TSH 的增加有增高的趋势，我们得出当 TSH 在正常范围内增高时，高胆固醇血症的患病率有增高的趋势。

表格二到六中的数据是按照不同模型的参数构建的，为了便于分别观察 TSH 与 TC、高胆固醇血症患病危险度以及其他血脂成分的关系，我们将表格中的数据重新归纳总结如下：

1. TSH 和 TC

我们此次研究的重点是 TSH 和 TC 的相关性，而且是要在各组的甲状腺激素以及其他变量均衡的条件下分析两者的关系。所以在很多分析中我们都是建立了两个模型来分步校正甲状腺激素的作用。首先通过偏相关分析，我们发现校正了性别、年龄、吸烟史、血糖和 BMI（模型一）后，TSH 和 logTC 之间是存在正性相关的，偏相关系数为 0.045（P=0.008）；进一步在模型二中我们又校正了甲状腺激素（通过提取的三个因子）后，r=0.049（P=0.004）（见表 2）.（模型一和模型二的变化趋势是一致的，只是由于多校正了甲状腺激素这个因素，数值会有稍微的变化。为了和我们的研究目的相契合，我们之后的结果描述都是分析所有因素均校正的结果。）为了进一步分析两者的线性趋势，在一般线性模型中，我们将 TSH 作为分组变量（分成六组），校正了其他混杂因素后，发现六个组的 logTC 的总体差别有统计学意义，logTC 随着 TSH 分组的线性变化系数为 0.017，p 值为 0.021(见表 3) 。通过前两种模型的分析我们发现 TSH 和 TC 之间有正相关性，为了进一步分析他们之间的数量依存关系我们建立了多元线性回归模型。多元线性回归模型中，校正了所有混杂因素后，logTC 和 TSH 的偏回归系数为 0.003，P值为 0.006(见表 4)，即 TSH 每增高 1 m IU/L，总胆固醇增加 1.006 mmol/L。通过以上三种模型分析 TSH 和 TC 的关系，结果均发现校正了所有混杂因素后（包括甲状腺激素）TSH 和 TC 之间存在有统计学意义的正性相关，即随着 TSH 的增加，TC 是逐渐增加的；甲状腺激素的校正虽然会对结果产生轻微影响，但是不改变总体的变化趋势（见图 1-4)。

在多元线性回归模型中，我们发现年龄和 TC 的标准化偏回归系数为 0.314（见图 4)，在所有校正的混杂因素的偏回归系数中是最大的，为了进一步探讨 TSH 与总胆固醇随着年龄的增长，它们之间的关系是否有变化，我们分

年龄组进行了偏相关分析，结果显示在50岁之前，两者关系变化不明显，但是当年龄大于50岁后，随着年龄的增大，TSH与总胆固醇的偏相关系数增加趋势明显（见图六），需要进一步做相关的研究进行证实。

总之，通过上述几种不同的统计分析方法，我们从不同的角度分析了TSH和TC之间的关系，最后得出的结果是一致的，即TC和TSH之间是存在正性相关性的，而且是不依赖于甲状腺激素的。

2. TSH与其他血脂成分

在偏相关分析（模型二）中，TSH和log转换后的LDL-C、HDL-C以及TG的偏相关系数分别为0.049（P=0.005），-0.004（P=0.818），0.059（P=0.000），与在模型一中的结果基本一致，不过HDL-C的变化比较大，由正值变为了负值，但是尚不具有统计学意义（见表2）。通过一般线性模型分析，我们得到TSH和log转换后的LDL-C、HDL-C以及TG的线性系数分别为：0.011（p=0.281），-0.006（p=0.529），0.074（p=0.001），趋势和偏相关分析是一致的。在多元线性回归分析（模型二）中，TSH和log转换后的LDL-C以及TG的偏回归系数分别为0.005（P=0.008），0.013（P=0.001），也就是说TSH每增高1 m IU/L，LDL-C以及TG分别增加1.012 mmol/L和1.030 mmol/L。多元线性回归模型中，分析TSH和HDL-C时只有性别、BMI、甲状腺激素可以进入模型，所以无法得到logTC和TSH的偏回归系数。

3. TSH和高胆固醇血症

根据NCEP/ATPIII我们将人群分成高胆固醇血症组和非高胆固醇血症组，并作为logistic分析的因变量，来比较按照TSH分成的6个组的患病危险度。将六个组的高胆固醇血症的患病率绘成折线图（图五），可见随着TSH的增加，高胆固醇血症的患病率有增高的趋势，只是尚无统计学意义（P=0.322）。在logistic回归模型中，将性别、年龄、BMI、吸烟史和血糖作为混杂因素校正后，得到TSH第二组到第六组与第一组比较的优势比（OR）分别为1.824、2.037、1.925、2.105和3.239；在上述模型的基础上再校正了甲状腺激素后，优势比分别为1.803、2.012、1.909、2.104、3.194，比未校正甲状腺激素时优势均有所降低，但是总体趋势不变（见表五）。根据上述统计结果可以得出，随着TSH的增加，高胆固醇血症的患病率的危险度总体上有逐渐增高的趋势，虽然

第四组较第三组有所降低，而且这种趋势在校正了甲状腺素激素的作用后依然存在。

讨论

我们通过对3664例甲状腺功能正常人群的血脂分析，发现正常参考范围的TSH和血脂有一定的相关性，而且年龄增高时，这种相关性更加明显。具体来说，通过偏相关分析，一般线性模型，多元线性回归模型和Logistic回归模型分析，我们发现TSH和总胆固醇、低密度脂蛋白、甘油三酯以及高胆固醇血症患病的危险度是有正相关性的，而且在校正了甲状腺激素的作用后，这种相关性依然存在。在多元线性回归模型中，我们发现甲状腺激素和总胆固醇是负相关的,即随着甲状腺激素的增加，总胆固醇是有降低的趋势的。据我们所知，我们的研究是唯一在研究甲状腺功能正常时，校正甲状腺激素的作用后，分析TSH和胆固醇的关系的研究。这也是我们研究的创新之处。这样的结果也验证了我们起初的假设,就是TSH和血清胆固醇的相关性是不依赖于甲状腺激素的。

以前的研究发现，正常参考范围的TSH与总胆固醇、甘油三酯和低密度脂蛋白胆固醇是正相关的，和高密度脂蛋白是负相关的。我们的研究结果与他们的研究结果基本一致[19-20]。HUNT研究发现甲状腺功能正常人群按照TSH亚分组后，TSH与TC、LDL-C和TG是正性相关，和HDL-C呈负性相关，即当TSH在正常范围增高时，一些不良的脂质成分（冠心病的危险因子）会随之增加，而且这种线性趋势可以扩展到整个TSH的分布[19]。PallasD[20]等的研究发现甲状腺功能正常的高胆固醇血症患者血清的TSH明显增高，也就是说TSH增高，高胆固醇血症的患病危险性增高；在hunt研究中，当TSH在正常参考范围高值时没有发现明显的血脂随之增高的迹象，而是一直呈线性相关，尽管他们的研究不能排除TSH和血脂的相关性是由于一些潜在的存在自身免疫性抗甲状腺抗体人群的存在。一篇关于TSH和低密度脂蛋白的研究发现[21]，甲状腺功能正常人群的TSH和胰岛素的敏感性没有相关性，但是TSH和LDL-C,TC,non-HDL-C是有统计学意义的正相关，并且这种正相关是由M/I值修饰的，而TSH与HDL-C是呈负相关的。

Nicole S. Nader[21]关于2-18岁人群的研究也有类似的发现,校正了性别、年龄和BMI后，研究发现TSH和甘油三酯仍呈正相关，但是与TC,HDL-C,LDL-C没有发现有统计学意义的相关性。此外，一项对韩国2205例绝经后的甲功正

常的妇女的研究发现，TSH 与 TC、LDL-C、TG 正相关，与 HDL-C 呈负相关，但是均无统计学意义，TSH 正常高组发生代谢综合征的危险性是 TSH 低组的 1.95 倍。Jose de Jesus Garduno-Garcia[26]等对 3148 例甲状腺功能正常的西班牙人群的研究发现，TSH 和 TC、TG 在校正了性别和年龄后依然呈正相关。

我们的研究结果与上述关于甲状腺功能正常人群的研究的文献报道基本一致，只是 HDL-C 和 TSH 的负性相关关系尚不具有统计学意义，这与一些既往的研究[25,28]是一致的，可能与我们的研究人群范围尚不够广泛有关，有待于进一步的研究来探讨。

我们的研究发现甲状腺激素和总胆固醇是有负相关性的，这与既往研究甲状腺功能低下时[1-3]，血脂成分的改变是一致的，而且我们此次研究是将甲状腺激素限定在正常参考范围，也就是说，甲状腺激素的作用可以扩展到甲功正常人群，作用是线性一致的。这与 Annemieke Roos[31]等的研究结果是一致。在建立多元线性回归模型时，由于一些主要影响因素没有进入模型，影响模型的建立，并且导致一些因子的效应出现不符合实际的情况，例如甲状腺激素对于 TG 和 LDL-C 的偏回归系数都为正值，这与既往的一些研究是不相符合的[21,31,21]，但是有的文献也有类似的报道[26, 32, 30]。正常参考范围的甲状腺激素对于 LDL-C 、HDL-C 和 TG 的作用有待于进一步的研究。

甲状腺功能异常时，血脂的组成成分会发生变化，这主要是由于血清甲状腺激素浓度发生了变化引起的。甲状腺激素的作用主要体现在以下几个方面：一、甲状腺激素增加胆固醇合成关键酶 HMG CoA 还原酶的活性，使得肝脏新合成的胆固醇增加[36]；二、增加细胞表面的 LDL 受体，导致 LDL 代谢增加[37]；三、增加胆固醇及其代谢产物从胆汁的排泄[38]；四、增加胆固醇酯转运蛋白[39]的活性；五、增加脂蛋白脂酶活性[40]。甲状腺激素主要是通过以上途径影响血清胆固醇的代谢。所以当甲状腺功能出现异常时，血脂会出现相应的变化。

Surks MI 等[41]的研究发现 TSH 位于正常高值的人群更容易出现甲状腺功能异常的早期症状。Whickham 20 年的随访研究发现 TSH 高于 2mU/l 的人群，更容易在血清中出现抗甲状腺抗体，进而发生甲低的危险性更大[42]。既往的观点更偏向于认为正常高值的 TSH 最终还是通过影响甲状腺激素水平来影响血清胆固醇的水平。有研究[30]报道正常范围 TSH 和 FT4 在校正了性别和年龄后也

是存在负相关的（β=-0.091，*P*=0.003）。我们的研究考虑了正常参考范围的TSH水平会有不同的甲状腺激素水平，如果不校正甲状腺激素水平，最终的胆固醇变化很可能是由于甲状腺激素的不均衡引起的。所以我们的研究在进行各种统计学分析时，均考虑了甲状腺激素这个混杂因素的影响，对T3和T4进行了校正。最终我们得到的结论是所有甲状腺功能正常人群，在权衡了可能会影响血清胆固醇浓度的因素后，TSH 和血清胆固醇水平有一定的相关性，患高胆固醇血症的危险性更高。这样的结果不是甲状腺激素的作用可以解释的，hunt研究也提出了同样的疑问[19]。

甲状腺激素对血清胆固醇的影响在我们的研究中是被校正了，所以不同TSH 水平引起的血清胆固醇的变化以及高胆固醇血症的患病率与甲状腺激素的关系就很小，更多的是TSH的不同。这就提示我们，TSH可以不依赖于甲状腺激素的作用通路直接作用于胆固醇的代谢。关于这方面的基础研究很少，有一篇文献中写到TSH可以上调肝脏细胞的HMGCR的表达来直接影响胆固醇的代谢[13]。我们的研究是基于3664例一般人群的回顾性调查研究，只是探讨了在正常范围内的 TSH 和胆固醇的变化，他们之间的相互作用机制的探讨有赖于更为严谨的实验设计。

我们通过对3664例甲状腺功能正常人群的资料的回归性研究发现：校正了性别、年龄、BMI、吸烟史、空腹血糖和甲状腺激素等混杂因素后，正常参考范围的血清 TSH 和血清 TC、LDL-C、TG 是存在正向相关性的，而与 HDL-C 的负性相关性尚不具有有统计学意义，也就说TSH和血脂的相关性可以扩展到正常参考范围，且这种相关性不依赖于甲状腺激素。

结论

通过对3664例甲状腺功能正常人群的血脂分析，发现正常参考范围的TSH和血脂有一定的相关性，而且年龄增高时，这种相关性更加明显。具体来说，通过偏相关分析，一般线性模型，多元线性回归模型和Logistic回归模型分析，我们发现TSH和总胆固醇、低密度脂蛋白、甘油三酯以及高胆固醇血症患病的危险度是有正相关性的，而且在校正了甲状腺激素的作用后，这种相关性依然存在。

The relationship between serum lipid and TSH within the referrence range in euthyroid population

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1.Introduction

Thyroid function is associated with lipid metabolism. Hypothyroidism is often accompanied by serum lipid concentrations that are associated with increased risk of cadiovascular disease[1-3]. Recent researcher find that subclinical thyroid diaseases can also influence the level of serum cholesterol. In several cross-sectional studies, subclinical hypothyroidism, an asymptomatic state characterized by normal serum concentrations of free T4 and slightly elevated serum concentrations of TSH, was found to be associated with a variable and somewhat inconsistent increase in TC and in LDL-C [6-9] and inconsistent changes in serum levels of HDL-C [8-17]. Serum choleaterol may be associated with thyrotrophin (TSH) even if the TSH is narrowed within the reference range[18-22, 23-29]. Above all, we conclude that the change of cholesterol is consistent with TSH whether the thyroid hormones are normal. However, there is a lack of clinical study which considers thyroid hormones as confounding factors. As we know, thyroid hormones are negatively associated with TSH[30], besides, some studies have found there is association between thyroid hormones and serum lipid[21,26,24,30,31,32]. Based on these reasons, we define thyroid hormones as confounding factors. In our retrospection research, we focus on the association of serum cholesterol and TSH within the reference range after adjustment of thyroid hormones.

2. Materials and Methods

2.1 Subjects and Measurement

We retrospectively reviewed 4848 subjects who were self-referred for a rountine health

check-up at Provincial Hospital affiliated to Shandong University (Jinan, China) from January 2004 to December 2009. All paticipants were asked to complete a self-reported questionnaire and provide an overnight fasing blood sample between 09:00 and 10:00 AM. The Ethics Committee of our institution approved this study and all subjects provided written consent.

We exclude the persons in non-euthyroid status and those using thyroid medication to gain the euthyroid population. Besides, to avoid the influence of confounding factors, the following subjects were also excluded: subjects with chronic liver disease or chronic renal disease, subjects with any disease that might affect thyroid metabolisim and lipid metabolism. After regression analysis of two variables by one factor, we exclude the subjects in which absolute value of residual standard deviation is less than 3. Finally, 3664 euthyroid general population were evaluated.

2.2 Anthropometric Measurements and Laboratory Methods

Weight and height were measured in Kg and cm respectively, and the body mass index (BMI) was calculated by dividing the weight (Kg) with the square of height (m2). Gender, age, smoking status and other essential information were gained from the self-reported questionnaire.

Serum FPG, TC, TG, LDL-C and HDL-C were measured using enzymatic methods with Olympus reagents by automated spectrophotometry performed on the Olympus AU5400 system (Olympus Corporation, Tokyo, Japan). Serum TSH, FT3, FT4, TT3 and TT4 were assayed using the Advia Centaur XP (Siemens Healthcare Diagnostics Inc, Tarrytown, USA) and its mating kits. All measurements were perfomed at clinical laboratory of Provincial Hospital affiliated to Shandong University.

The reference range were 3.9-6.3 mmmol/L (FPG), 3.6-6.2 mmol/L (TC), 0.5-3.36 mmol/L (LDL-C), 0.8-1.5 mmol/L (HDL-C), 0.4-1.8 mmol/L (TG); 0.35-5.5 m IU/L (TSH) , 3.5-6.5 pmol/L (FT3) , 11.5-22.7 pmol/L (FT4) ,0.92-2.79 ng/mL (TT3) ,58.1-140.6 ng/mL(TT4).

2.3 Definitions

Euthyroidism was defined as an FT4 level between 11.5 and 22.7 pmol/l with a

TSH level between 0.27 and 5.5 m IU/l. Hypercholesteria was defined in accordance with the National Cholesterol, Education Program, Adult Treatment Panel III criteria (NCEP/ATPIII): total cholesterol >6.2 mmol/l.

2.4 Statistical analysis

As there exists colinearity among FT3、FT4、TT3 and TT4, 3 principal components (factor1,factor2,facor3) are extracted to adjust the effects from thyroid hormones (variance contribution rate: 87.729%) [33]. The equations are as follows:

$$\text{Factor1} = 0.192\times\frac{FT_3-4.9869}{0.65884}+0.392\times\frac{FT_4-17.4741}{2.66429}+0.464\times\frac{TT_3-1.3610}{0.45369}+0.468\times\frac{TT_4-98.3905}{25.94527}$$

$$\text{Factor2} = 0.701\times\frac{FT_3-4.9869}{0.65884}+0.402\times\frac{FT_4-17.4741}{2.66429}-0.253\times\frac{TT_3-1.3610}{0.45369}-0.375\times\frac{TT_4-98.3905}{25.94527}$$

$$\text{Factor3} = 0.552\times\frac{FT_3-4.9869}{0.65884}-0.766\times\frac{FT_4-17.4741}{2.66429}+0.641\times\frac{TT_3-1.3610}{0.45369}-0.221\times\frac{TT_4-98.3905}{25.94527}$$

The 3664 subjects were divided in six groups according to serum TSH levels within the reference range:<2.5 percentile, >97.5 percentile, and quartiles with the 2.5–97.5 percentile range[35]. Actually, they were classified as follows: group 1, 0.27 m IU/L≤TSH < 0.62 m IU/L ;Group 2, 0.62 m IU/L≤TSH < 1.36 m IU/L ;Group 3,1.36 m IU/L≤TSH < 1.93 m IU/L ;Group 4, 1.93 m IU/L≤TSH < 2.66 m IU/L; group 5, 2.66 m IU/L≤TSH < 4.61 m IU/L; Group 6, 4.62 m IU/L≤TSH≤5.50 m IU/L.

The 6 subgroups are expressed as mean±SD for continuous variables and as numbers or percentages for categorical variables. FPG, TC, LDL-C, HDL-C and TG that were not normally distributed were logarithmically transformed before analyses were made. Relations between TSH levels and lipids were analyzed by partial correlation analyses, general linear analysis, multivariate logistic regression analysis and multiple linear regression analysis.2 models were constructed in order to compare and adjust the effect of thyroid hormones: Model 1 was adjusted for gender,age, smoking status, BMI and FPG; Model 2 added thyroid hormones besides the factors in Model 1. Multivariate logistic regression analysiswas carried out to calculate the odds ratios (ORs) of having hypercholesterolemia in the presence of serum TSH compared to group 1(TSH catagories). We further explored whether the association between TSH

and cholesterol level differed according to age groups. A 2-sided *P* value of <0.05was considered statistically significant. Statistical analyses were performed using SPSS software (version 17.0,Jinan,China).

3 . Results

The characteristics of the study subjects which were divided into 6 groups according to the TSH were listed in Table 1. There were significant differences in the composition of gender、smoking status and means of age、FPG、HDL-C、FT3、FT4、TT3、TT4 across the six groups, while other parameters had no statistically significant difference. The baseline characteristic of thyroid hormones was unbalance, which validated the necessity of the adjustment.

The results unfolded in the tables (2-5) were exhibited depending on the different statistical models. In order to observe the association between TSH and TC、hypercholesteremia、LDL-C、HDL-C and TG, we summarized the analysis results as follows:

3.1 TSH and TC

What we focused on was the relationship between TSH and TC, then let's see their results firstly. Through partial correlation analysis (model 1), the partial correlation coefficient between TSH and logTC was 0.049 (*P*=0.004);furthermore, we adjusted thyroid hormones(in the form of 3 principal components),then r=0.049 (*P*=0.004) (table 2) .The results in model 2 were consist with that in model 1, but the values changed a few. In order to match our research, we represent the results in model 2. We further explored the trend of TC across the 6 groups of TSH in general linear analysis. The differences of logTC across the 6 groups of TSH reached statistical significance, and the linear coefficient was 0.017 (*P*=0.021)(table 3). The former 2 analysis showed positive association between TSH and TC, still we constructed multiple linear regression model to study the quantities realationship. After all confounding factors considered, the partial regression coefficient between logTC and TSH was 0.003(table 4), which meant TC increased 1.006 mmol/l as TSH increased 1

m IU/l. Above all, after adjustment of confounding factors, TSH showed a positive correlation with TC, although thyroid hormones could influence the results, but the trend still existed(figures1-4).

Multiple linear regression analysis indicated the partial regression coefficient between logTC and age was 0.314, which account for the the highest flight of the confounding factors. In order to analyse the relationship between TSH and TC with age, we divided the population into 6 subgroups according to age to compute the partial correlation coefficient in the 6 subgroups (table 6) . The current of change across the 6 subgroups was illustrated in Figure 6, from which we can detect an ascending trend. Particularly, the relationship between TSH and TC was notobvious if the persons were younger than 50 years old, but the relationship became distinct in the elder population. The result suggust that TSH showed more positive correlation with TC as the age became elder, which still needed more research.

3.2 TSH and other lipids

In partial correlation analysis(model 2), the partial correlation coefficients between TSH and the log transform of LDL-C,HDL-C and TG were 0.049（P= 0.005），-0.004（P=0.818），0.059（P=0.000）(table 2). In general linear analysis,the linear coefficient were 0.011(p=0.281), -0.006（p=0.529）and 0.074（p=0.001）respectively(table3),which was consist with the partial correlation analysis. In multiple linear regression analysis, TSH was positive with LDL-C and TG, whose regression coefficients were 0.005(P=0.008) and 0.013（P=0.001）. That meant TC increased 1.012 mmol/l and 1.030 mmol/l as TSH increased 1 m IU/l. However, HDL-C couldn't enter the multiple linear regression analysis, so we missed the regression coefficient of HDL-C and TSH.

3.3 TSH and hypercholesteremia

As described in figure 5, the prevelance of hypercholesteremia in the 6 groups were showed a rising trend, but the difference made no statistically sense(P=0.322). Furtherly, we analyse the OR values in the 2 to 6 groups with or without thyroid hormones adjusted in different models. The OR values were 1.824、2.037、1.925、

2.105、3.239 in model 1 and 1.803、2.012、1.909、2.104、3.194 in model 2 respectively when group 1 was defined as reference group. Results between two models had a few difference, but the increasing tendency still existed (the trend in group 3 and 4 was not so obvious). We concluded that the prevelance of hypercholesteremia increased as TSH value mounted up even if the effect of thyroid hormones was equipoised.

Discussion

In this study, we explore the relationship between TSH and serum lipid through the data from 3664 euthyroid subjects. We found there were positive associations between TSH and TC、LDL-C、LDL-C、TG、hypercholesteremia. Moreover, the relationship still remained the same after thyroid hormones adjusted. Beyond those results, we also discovered that TC showed a negative relationship with thyroid hormones in the multiple linear regression analysis. Finally, our data showed that TSH within the reference range was related with components of lipids. Besides, the correlation was stronger when the age became elder. This study is, to our knowledge, the first that addresses the possible linkage between TSH within reference range and serum lipids after the adjustment of thyroid hormones. This is the innovation of our research, and the results illustrated above are consistent with the hypothesis mentioned in the introduction.

Several studies have looked into the possibility of an association between the TSH and serum lipids,which got the similar results with us[19-29]. PallasD et al. found that many hypercholesterolemic persons with thyroid tests within the conventional normal range may have a slight impairment of their thyroid function [20]. That is to say, the occurrence of hypercholesteremia increased as the TSH increased. Significant age- and sex-adjusted partial correlations of TSH with LDL-C (r =0.48; P=0.01) and HDL-C (r=-0.36; P=0.05) were observed by Bakker SJ [21], importantly, the effect-modification of the association of TSH with LDL-C by insulin sensitivity suggests that insulin-resistant subjects are most susceptible to this increased risk. Another study about 3148 euthyoid subjects showed that serum TSH values showed a positive correlation (adjusted for age and sex) with total cholesterol, triglycerides[26].

The HUNT study found that total serum cholesterol, LDL cholesterol, non-HDL cholesterol and triglycerides increased consistently with increasing TSH and that HDL decreased consistently[19]. Furthermore, the association with serum lipids was linear across the entire reference range of TSH. Our research gained analogous results with those studies, except that HDL-C with no significance. This may be due to our relative small population.

We have demonstrated an negative associtionbetween TC and thyroid hormones within the normal reference range, in accordance with the earlier observed association between hypothyroidism and hyperlipidemia. Annemieke Roos et al.[31] got the similar results, which showed that the influence of thyroid function on lipid metabolism extended into the euthyroid range. In multiple linear regression analysis, the coefficients between thyroid hormones and TG、LDL-C were positive,which was contradictory to the previous studies[21,31,24]. Nevertheless, relationship in other articles was consistent with our findings[26, 32, 30]. The controversial was still existing in euthyroid subjects, and further research should be performed to assess the correlation.

The primary mechanism for hypercholesterolemia in hypothyroidism is accumulation of LDL cholesterol due to a reduction in the number of cell surface receptors for LDL [37], resulting in decreased catabolism of LDL. Other mechanisms also may aff ect the serum cholesterol concentration in hypothyroidism: diminished secretion of ch olesterol into bile has been demonstrated in hypothyroid rats [38]. Reduced cholesteryl ester transfer (the net transfer of cholesterol from HDL to LDL and very-low-densi ty -lipoprotein [VLDL]) in hypothyroidism may minimize the increase in serum LDL cholesterol concentrations [39].A different mechanism,reduced lipoprotein lipase act ivity, is responsible for the development of hypertriglyceridemia in hypothyroidism [40]. However, hepatic-hydroxy- methyl- glutaryl coenzyme A reductase activity was lower in hypothyroidism[36],which reduced the new synthsis of cholesterol.the five mechanisim determined the final concentration of cholesterol in total.

Surks MI et al. found that many people with TSH in the upper part of the

reference range are likely to display early signs of thyroid dysfunctio[41].Results from 20 years of follow-up of the Whickham Study indicated that TSH higher than 2 mU/l was associated with increased risk of hypothyroidism [42]. Previous studies tend to impute different cholesterol level to thyroid hormones.yet some study have cover that TSH showed negative association with FT4 in euthyroid people with gender and age adjusted(β=-0.091, P=0.003). Our research root out unbalance thyroid hormones levels even if the TSH is within normal range. The confounding effect resulted from thyroid hormones must be counteracted, or the final difference of TC may be due to thyroid hormones. This is the main reason that we constructed two models to demonstrate the thyroid hormones. We conclude that TSH is associated with serum cholesterol levels in euthyroid population, which is independent on thyroid hormones. In line with the HUNT study, they also got the similar results.

3 principal components are extracted to adjust the effects from thyroid hormones, which could stand for 87.729 percentage of thyroid hormones. The only difference across the six groups is the difference level of TSH. This result prompt a new idea that TSH can influence the metabolism of cholesterol directly, without depending on thyroid hormones. Few research talk about this study, only one article mentioned that TSH could up-regulate hepatic HMGCR expression, which indicated a potential mechanism for hypercholesterolemia involving direct action of TSH on the liver[43].

We studied the relationship between TSH and serum lipid through the data from 3664 euthyroid subjects and found there were positive associations between TSH and TC、LDL-C、LDL-C、TG、hypercholesteremia after gender, age, BMI, smoking status, FPG and thyroid hormones adjusted . Our data addresses the possible linkage between TSH within reference range and serum lipids after the adjustment of thyroid hormones. Besides, the correlation was stronger when the age became elder.

Conclusion:

In this study, we explore the relationship between TSH and serum lipid through the data from 3664 euthyroid subjects. We found there were positive associations between TSH and TC、LDL-C、LDL-C、TG、hypercholesteremia. Moreover, the

relationship still remained the same after thyroid hormones adjusted. Beyond those results, we also discovered that TC showed a negative relationship with thyroid hormones in the multiple linear regression analysis. Finally, our data showed that TSH within the reference range was related with components of lipids. Besides, the correlation was stronger when the age became elder. This study is, to our knowledge, the first that addresses the possible linkage between TSH within reference range and serum lipids after the adjustment of thyroid hormones.

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附 表

TABLE1. Population characteristics of 3664 euthyroid subjects from the general population, including statistical comparison ofcharacteristics of subjects across the categories of thyroid stimulating hormone (TSH) within the reference range(0.27–5.5m IU/l)

[a] Statistical comparison of characteristics of subjects among catagories of TSH

characteristic	TSH(mmom/l)						*p*
	0.27-0.61	0.62-1.35	1.36-1.92	1.93-2.65	2.66-4.60	4.61-5.50	
gender							
male	62	513	447	389	315	21	
female	50	362	421	495	535	54	
all	112	875	868	884	850	75	0.000
smoking status							
none	77	595	630	708	720	67	
occasional	5	62	52	47	40	2	
often	30	218	186	129	90	6	0.000
hypercholesteremia							
No.	12	136	140	130	138	17	
others	100	739	728	754	712	58	
prevalence rate(%)	10.71	15.54	16.13	14.71	16.24	26.67	0.322
BMI（kg/m2）	25.01±3.56	25.28±3.72	25.09±3.50	24.85±3.71	24.89±3.67	25.13±3.11	0.162
age（yr）	51.30±13.38	48.82±13.22	47.84±14.06	46.16±13.93	47.01±13.71	49.17±14.09	0.000
FPG (mmol/liter)	5.73±1.57	5.50±1.43	5.41±1.41	5.35±1.30	5.31±1.32	5.15±0.90	0.002
TC (mmol/liter)	4.98±0.91	5.21±0.98	5.24±0.97	5.24±0.99	5.25±1.03	5.32±1.08	0.131
LDL-C (mmol/liter)	2.94±0.74	3.04±0.77	3.07±0.76	3.05±0.78	3.06±0.81	3.01±0.76	0.665
HDL-C (mmol/liter)	1.43±0.35	1.42±0.35	1.44±0.35	1.48±0.35	1.48±0.35	1.44±0.34	0.000
TG (mmol/liter)	1.38±0.88	1.67±1.53	1.57±1.29	1.56±1.37	1.55±1.42	1.90±2.60	0.080
FT3 (pmol/liter)	5.22±0.75	5.08±0.72	4.98±0.65	4.97±0.60	4.89±0.64	5.00±0.65	0.003
FT4 (pmol/liter)	18.03±2.87	17.97±2.66	17.57±2.66	17.40±2.54	16.78±2.63	16.90±2.69	0.000
TT3 (ng/mliter)	1.63±0.50	1.45±0.48	1.33±0.41	1.35±0.50	1.28±0.39	1.21±0.37	0.000
TT4 (ng/mliter)	120.39±35.42	100.70±29.18	98.33±24.04	98.95±24.36	94.10±23.91	88.27±12.20	0.000

TABLE 2. Different factors adjusted partial correlations of TSH with log transformation of TC 、LDL-C 、HDL-C andTG

Paramater	Model 1		Model 2	
	r	*P*	r	*P*
logTC	0.045	0.008	0.049	0.004
logLDL-C	0.044	0.011	0.049	0.005
logHDL-C	0.001	0.960	-0.004	0.818
logTG	0.058	0.001	0.059	0.000

Model 1,after adjustment for gender,age,smoking status, FPG and BMI; Model 2,after adjustment for gender,age,smoking status, FPG,BMI and thyroid hormones.

TABLE 6. Partial correlations of TSH with log transformation of TC according to categories of age

age (years)	R	*P* value
12-29	0.053	0.278
30-39	0.018	0.667
40-49	0.035	0.28
50-59	0.032	0.346
60-69	0.072	0.112
70-93	0.133	0.054

Adjusted for gender, age, BMI, smoking status and FPG, and thyroid hormones;

Table3 Means of log transformation and geometric means of serum lipids (mmol/l) according to categories of thyroid stimulating hormone
(TSH) within the reference range(0.27–5.5m IU/l) in the 3664 euthyroid subjects

	TC		LDL-C		HDL-C		TG	
Paramater	logTC	TC	logLDL-C	LDL-C	logHDL-C	HDL-C	logTG	TG
TSH(mIU/l)				**Model 1**				
0.27-0.61	0.716	5.20	0.481	3.03	0.146	1.40	0.164	1.46
0.62-1.35	0.735	5.43	0.495	3.13	0.142	1.39	0.209	1.62
1.36-1.92	0.740	5.50	0.503	3.18	0.146	1.40	0.207	1.61
1.93-2.65	0.742	5.52	0.505	3.20	0.152	1.42	0.214	1.64
2.66-4.60	0.740	5.50	0.505	3.20	0.149	1.41	0.222	1.67
4.61-5.50	0.740	5.50	0.493	3.11	0.135	1.36	0.279	1.90
P	0.019		0.107		0.383		0.030	
Linear coefficient	0.017		0.011		-0.003		0.074	
P for linear	0.021		0.300		0.730		0.001	
TSH(mIU/l)				**Model 2**				
0.27-0.61	0.716	5.20	0.482	3.03	0.148	1.41	0.163	1.46
0.62-1.35	0.734	5.42	0.494	3.12	0.142	1.39	0.208	1.61
1.36-1.92	0.739	5.48	0.502	3.18	0.145	1.40	0.207	1.61
1.93-2.65	0.742	5.52	0.505	3.20	0.151	1.42	0.214	1.64
2.66-4.60	0.740	5.50	0.505	3.20	0.147	1.40	0.222	1.67
4.61-5.50	0.740	5.50	0.494	3.12	0.134	1.36	0.277	1.89
P	0.020		0.113		0.445		0.031	
Linear coefficient	0.017		0.011		-0.006		0.074	
P for linear	0.021		0.281		0.529		0.001	

Model 1,after adjustment for gender,age,smoking status, FPG and BMI; Model 2,after adjustment for gender,age,smoking status, FPG,BMI
and thyroid hormones.

TABLE4. Multivariate linear regression models of all paramaters as determinants of log transformation TC，LDL-C,HDL-C and TG concentrations

Values of B,unstandardized regression coefficients;95% CI of B, 95% confidence intervals of B;Values of β are standardized regression coefficients.

"/" means no association

paramater	logTC				logLDL-C			
	B	*P*	β	95%CI	B	*P*	β	95%CI
gender	0.021	0.000	0.128	(0.015, 0.027)	0.013	0.004	0.056	(0.004, 0.021)
age	0.002	0.000	0.314	(0.002, 0.002)	0.002	0.000	0.276	(0.002, 0.003)
BMI	0.002	0.000	0.085	(0.001, 0.003)	0.005	0.000	0.157	(0.004, 0.006)
smoking status	0.011	0.000	0.106	(0.007, 0.015)	0.012	0.000	0.084	(0.007, 0.018)
FPG	0.007	0.000	0.119	(0.005, 0.009)	0.008	0.000	0.099	(0.006, 0.011)
TSH	0.003	0.006	0.043	(0.001, 0.006)	0.005	0.008	0.043	(0.001, 0.008)
FAC-1	/	/	/	/	/	/	/	/
FAC-2	/	/	/	/	0.005	0.035	0.034	(0.010, 0.036)
FAC-3	-0.006	0.002	-0.049	(0.009, 0.002)	-0.01	0.000	-0.066	(-0.015, -0.005)

paramater	logHDL-C				logTG			
	B	*P*	β	95%CI	B	*P*	β	95%CI
gender	0.062	0.000	0.280	(0.055, 0.069)	-0.066	0.000	-0.126	(-0.084, -0.048)
age	/	/	/	/	0.002	0.000	0.117	(0.002, 0.003)
BMI	-0.008	0.000	-0.278	(-0.009, -0.008)	0.020	0.000	0.283	(0.004, 0.006)
smoking status	/	/	/	/	0.033	0.000	0.100	(0.022, 0.045)
FPG	/	/	/	/	0.035	0.000	0.181	(0.029, 0.040)
TSH	/	/	/	/	0.013	0.001	0.051	(0.006, 0.020)
FAC-1	-0.007	0.004	-0.045	(-0.011, -0.002)	/	/	/	/
FAC-2	/	/	/	/	0.014	0.008	0.040	(0.004, 0.025
FAC 3	/	/	/	/	/	/	/	/

TABLE 5. Odds ratio (OR) for hypercholesteremia (TC>6.2 mmo/l), by categories of TSH in 3664 euthyroid subjects from the general population

TSH(mmol/l)	model 1				model 2			
	B	*P*	OR	95%CI	B	*P*	OR	95%CI
0.27-0.61	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
0.62-1.35	0.601	0.07	1.824	(0.951, 3.496)	0.59	0.076	1.803	(0.939, 3.462)
1.36-1.92	0.711	0.032	2.037	(1.064, 3.901)	0.699	0.035	2.012	(1.049, 3.858)
1.93-2.65	0.655	0.049	1.925	(1.003, 3.695)	0.647	0.052	1.909	(0.993, 3.670)
2.66-4.60	0.744	0.025	2.105	(1.097, 4.040)	0.744	0.026	2.104	(1.095, 4.043)
4.61-5.50	1.175	0.006	3.239	(1.392, 7.538)	1.161	0.007	3.194	(1.367, 7.464)
P[a]			0.130				0.124	

Ref., Reference group.

Model 1 ,adjusted for gender, age, BMI, smoking status and FPG; Model 2 , Adjusted for gender, age, BMI, smoking status and FPG, and thyroid hormones ;

[a] *P* value for linear trend across the categories of TSH.

附 图

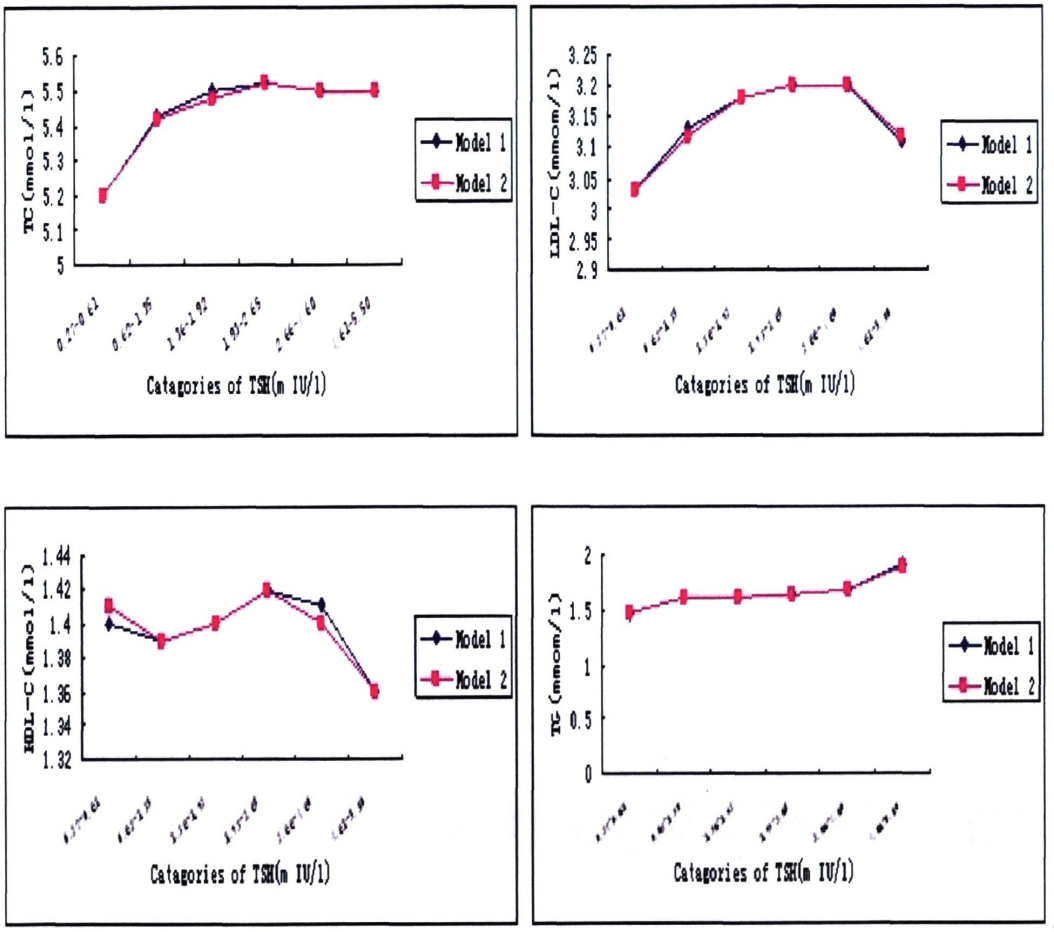

Figure 1-4 Geometric mean of TC、 HDL-C、 LDL-C and TG by categories of TSH within the reference range (0.27-5.50 mU/l),

Model 1,after adjustment for gender,age,smoking status, FPG and BMI; Model 2,after adjustment for gender,age,smoking status, FPG,BMI and thyroid hormones.

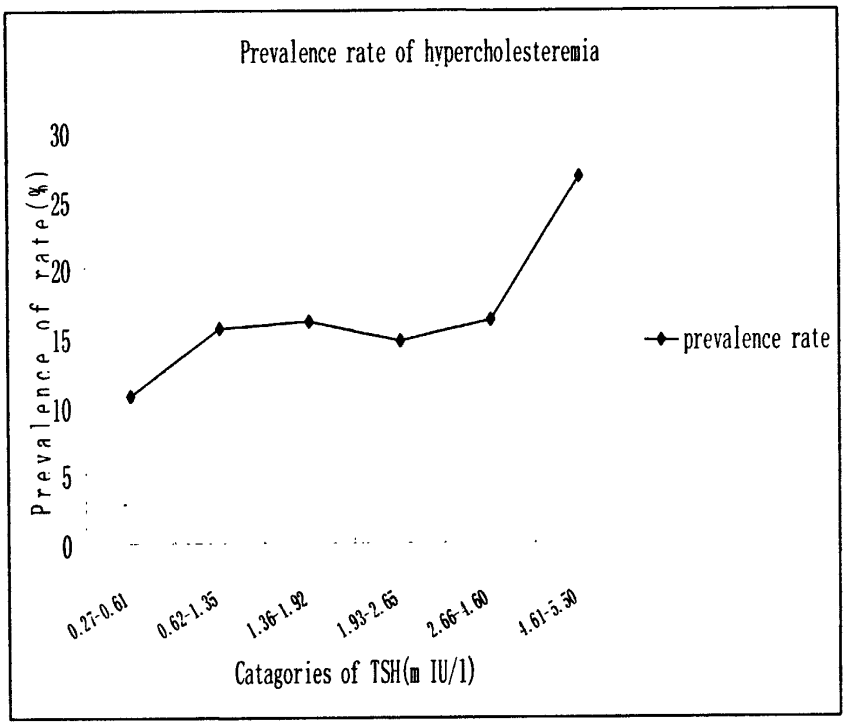

Figure 5 Prevalence rate of hypercholesteremia by categories of TSH within the referen--ce range (0.27–5.5 m IU/liter) in 3664 euthyroid subjects from the general population , no factors were adjusted.

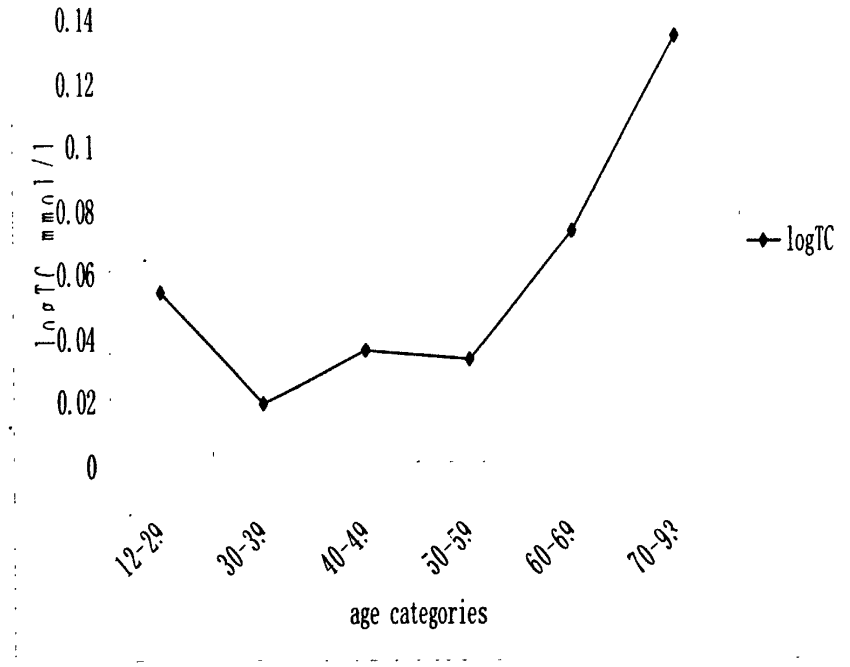

Figure 6 Partial correlations of TSH with log transformation of TC according to categories of age.

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备注					

※优秀为“A”；良好为“B”；合格为“C”；不合格为“D”。