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H. 知的所有権の出願・取得状況

なし。

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
小野　稔	補助循環の分類とその適応	上田裕一	心臓外科看護の知識と実際	MCメディカ出版	大阪府吹田市	2009	270-278

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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1 補助循環の分類とその適応

大動脈内バルーンポンプ
IABP
経皮的心肺補助装置
PCPS
補助人工心臓
VAD

補助循環とは，薬物療法では治療が不可能な重症心不全に対して，心臓のポンプ機能を機械で補助・代行する方法である．心筋梗塞などに伴う急性の心原性ショック，慢性心不全における心不全の急性増悪，開心術後の低心拍出量症候群などに対して使用する．現在，大動脈内バルーンポンプ（intraaortic balloon pump；IABP），経皮的心肺補助装置（percutaneous cardiopulmonary support；PCPS），補助人工心臓（ventricular assist device；VAD）などがあり，心不全の重症度・病態や予想される補助期間などによって使い分けている[1, 2]．

1 適　応

補助循環の適応となる疾患・病態を表1に示す．心筋梗塞やこれに伴う機械的合併症（心室中隔穿孔，心破裂，乳頭筋断裂）による心原性ショック，慢性心不全の急性増悪，急性心筋炎，開心術後の低心拍出量症候群などで，利尿薬・強心薬・血管拡張薬を投与しているにもかかわらず，表に示す血行動態から改善しない重症の心不全に対して使用する．

手技の容易さと患者に対する侵襲度の低さから，まずIABPを考慮する．IABPのみでは補助が不十分であるか，またはIABP禁忌の状態があれば，PCPSの使用または併用を考慮する．通常では，IABPは数日から1週間，PCPSは2週間以内の補助を行うことが多く，補助期間が長くなることが予想される場合や，PCPSでも補助が不十分と考えられる場合には，VADの装着を検討する必要がある．

圧力補助と流量補助 豆知識

補助循環装置は，血圧や血管抵抗を変化させて補助を行うIABPと，実際にポンプで血液を送り込むPCPSやVADに分けることができます．前者は圧力補助と呼ばれ，直接的に血液拍出量を増加させる効果はありません．後者は流量補助と呼ばれ，直接的に血液拍出量を増加させる働きがあります．

表　補助循環の適応

●補助循環の適応疾患・病態

1. 虚血性心疾患
   ①急性心筋梗塞合併症：心原性ショック，うっ血性心不全，心室中隔穿孔，乳頭筋断裂
   ②不安定狭心症（薬物治療では不十分と考えられる場合）
   ③高度の左主幹部病変
   ④虚血性心筋症による慢性心不全の急性増悪
2. 非虚血性心疾患
   ①重症心臓弁膜症による心不全（特に僧帽弁閉鎖不全症）
   ②特発性心筋症による心不全の急性増悪
   ③先天性心疾患による心不全の急性増悪
   ④劇症型心筋炎
3. 開心術周術期
   ①体外循環離脱困難症例
   ②開心術後低心拍出量症候群
   ③麻酔導入時における予防的使用（重症虚血性心疾患，重症心不全）
4. そのほか
   ①重症心疾患を合併した一般外科症例の麻酔・手術補助
   ②PTCA時の循環補助（supported PTCA）
   ③ほかの補助循環から離脱補助

●補助循環の適応血行動態

①収縮期血圧	90mmHg以下
②肺動脈楔入圧	20mmHg以上
③心係数	2.0L/min/m^{2}以下
④時間尿量	0.5mL/kg以下

大動脈内バルーンポンプ
IABP

2 大動脈内バルーンポンプ（IABP）

A IABPのしくみ

IABPは鼠径部の大腿動脈を穿刺し，近位下行大動脈にバルーン先端を留置する．挿入後は，必ずX線撮影を行って先端の位置を確認する．深すぎると大動脈の損傷，浅すぎると腹部臓器血流の障害を起こすことがある．心電図または動脈圧に同期させることによって，作動させる．IABPは同期するタイミングが正しくないと，かえって心臓に負担をかけることがある．心収縮期にバルーンをしぼませることによって，後負荷（心拍出抵抗）を軽減し（systolic unloading），心拡張期にバルーンを充満することによって拡張期圧を上昇させて冠動脈血流を増加させる（diastolic augmentation）働きをする．IABPバルーンの容量は20～40mLで，患者の体格や下行大動脈の大きさに応じて選択する．バルー

systolic unloading

diastolic augmentation

同期のタイミング　**check!**

IABPは，心電図または動脈圧に同期させることによって作動させます．同期するタイミングが正しくないと，かえって心臓に負担をかけることがありますので，特にペーシングや心房細動の症例では，常にタイミングに注意しておくことが必要です．

ン駆動はヘリウムガスによって行う．最近の新しい機種では，同期タイミングを自動的に検出できる機能が搭載されていて，ペーシングや心房細動であっても追随できる．離脱に際しては，補助回数とバルーン容量の両方を設定することができる．

B　IABPの禁忌

禁忌となる病態は，2度以上の大動脈弁閉鎖不全症，大動脈解離・胸部大動脈瘤，高度な大動脈粥状硬化症，高度な大動脈や腸骨・大腿動脈狭窄や閉塞症などがある．合併症としては，挿入時の大動脈・血管損傷（穿孔や解離），血栓塞栓症，下肢や腹部臓器の血流障害，カテーテル感染症，抜去後の止血不良に伴う血腫形成などがある．大動脈・血管損傷は致命的になり得るので，バルーンはガイドワイヤー補助下に抵抗なく挿入できることを確認しながら進める．透視下に行えばより安全である．

経皮的心肺補助装置
PCPS

3　経皮的心肺補助装置（PCPS）

A　PCPSのしくみ

PCPS装置はポンプ，人工肺，カニューレおよび回路から構成されている．IABP単独では補助が不十分と考えられる場合に，単独またはIABPと併用して使用する．大腿動静脈へのカニューレ挿入は，IABPと同様にセルディンガー法で穿刺し，ガイドワイヤー下に行う．循環虚脱などのために穿刺が困難な場合は，大腿動静脈を外科的に露出して行うこともある．大腿静脈から右心房まで入れたカニューレから脱血し，人工肺で血液を酸素化した後に，同側または対側の大腿動脈から返血する．患者の体格・血管径や必要とされるPCPS補助流量などに基づいて，送脱血それぞれのカニューレのサイズを選択する．回路全体がヘパリンコーティングされており，ヘパリンで活性凝固時間（activated

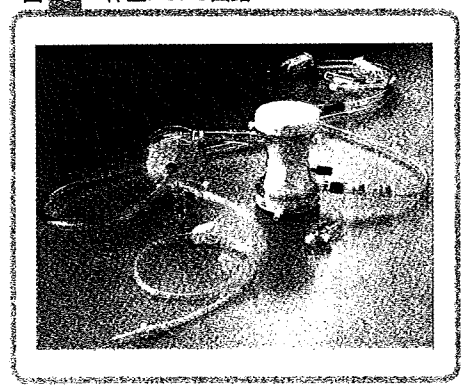
coagulation time；ACT）を150～200秒程度にコントロールする．また，最近は人工肺とポンプ回路が一体化しているので，回路のプライミングが短時間に容易に行える（図1）．

B　PCPSの適応と禁忌

PCPSの適応疾患・病態はIABPと大きくは違わないが，一般的にはIABPで十分に循環の補助ができない場合に，単独またはIABPと併用して使用する．PCPSでは，大腿動脈から逆行性に送血される．心臓が拍出する方向に対して逆に送血するため，心臓にはある程度の後負荷がかかる．左心室の後負荷軽減や冠血流を確保するためには，IABPを併用する必要がある．1～2週間補助しても改善が認められない場合は，VADの装着を考慮する．

禁忌となる病態としては，IABPとほぼ同様である．ヘパリンを使用するために，出血性合併症に注意する．ACTを1日2回以上測定し，適宜ヘパリン投与量を調節する．血小板の減少や凝固・線溶系の亢進のために出血傾向が出現し，濃厚血小板や新鮮凍結血漿の投与が必要になることもある．

図1　一体型PCPS回路



血漿露出　豆知識

PCPSでは膜型人工肺によって静脈血を酸素化して動脈へ送ります．人工肺は血液中の因子などと作用して機能が低下（劣化）して，微量な血漿成分が外へ漏れる減少（血漿漏出：serum leakage）が起こってきます．劣化の速度を抑えるために，1時間に1回人工肺への酸素送気量を急速に増やし（フラッシュ），酸素排出孔から水分を吹き飛ばします．

血栓予防・人工肺の保護のためには，なるべく高めのACTが安全である．送血カニューレの太さはIABPより太いために（13～19Fr.），下肢の虚血には注意が必要である．虚血を予防するために，送血カニューレの遠位側の大腿動脈へ留置針を挿入して，送血管の側枝から血液を灌流することがある．数日以上連続駆動するとポンプの劣化や溶血がみられるようになるので，人工肺とポンプの交換が必要となる．

補助人工心臓
VAD

4 補助人工心臓（VAD）[3, 4]

A VADの種類

人工心臓には，回復不可能な自己の心機能を完全に代行する全置換型人工心臓（total artificial heart；TAH）と，自己心機能の一部または大部分を代行することによって循環機能を補助するVADがある．TAHは日本では使用できない．VADには，ポンプ本体を体内に植込む体内植込み型と，ポンプを体外に出す体外設置型がある．わが国で最も多く使用されているのが，体外設置型の東洋紡国立循環器病センター型である．体外設置型としてBVS®5000も使用されている．植込み型には現在わが国で保険適用された機種はなく，ハートメイト（HeartMate®），エヴァハート（EVAHEART®），デュラハート（DuraHeart®），ジャービック2000（Jarvik®2000）の4種類が臨床治験中で，早期の認可が期待されている．

VADは，IABPやPCPSの単独または併用による補助では不十分と考えられる症例や，2～4週間を超える長期の補助が必要となる場合に使用する．左心補助（LVAD），右心補助（RVAD）および両心補助（BVAD）ができるが，LVADが最も多いのでここでは体外設置型LVADを中心に述べる．

B LVADのしくみ

LVADは，送血・脱血カニューレ，血液ポンプと駆動装置（コンソール）から構成されており（図2），通常は胸骨正中切開で人工心肺を使用して装着する．脱血カニューレは，左心室心尖部にカフを縫着して挿入する．左房脱血を行うこともあるが，開心術後の人工心肺離脱困難などの比較的短期の補助がよい適応となる．左室心尖脱血は補助血流量が安定して得られることが多く，血栓塞栓症は起こしにくいため，数カ月以

人工心肺離脱困難

図　補助人工心臓装置

a. 東洋紡国立循環器病センター型 VAD ポンプ　　b. 東洋紡国立循環器病センター型 VAD コンソール

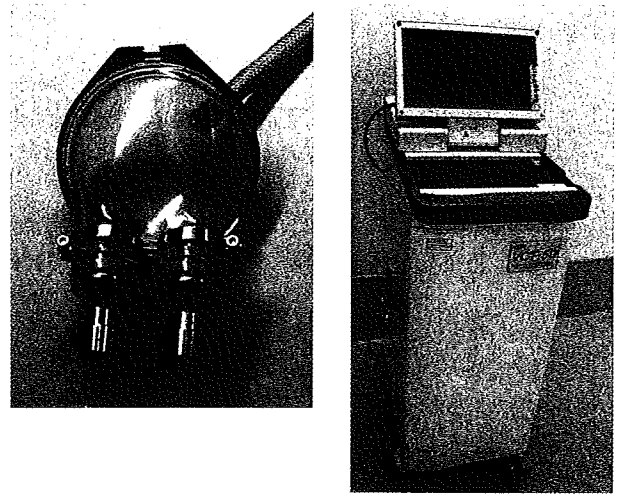
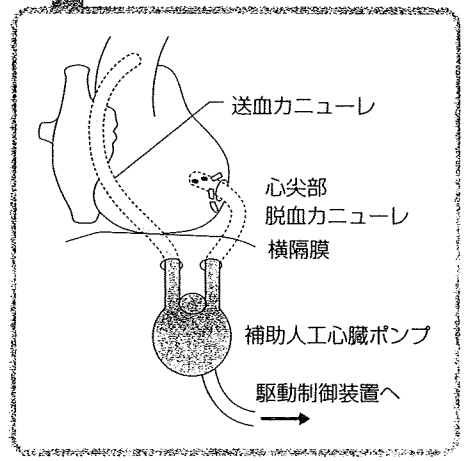


図　東洋紡国立循環器病センター型VAD装着イメージ図



上の長期の補助が必要な症例に適している．送血カニューレ先端の人工血管を上行大動脈に縫着して，ポンプから体へ送血する．

体外設置型では送血および脱血カニューレが皮膚を貫通し，血液ポンプに連結されている（図3）．ポンプ駆動は，体外にある駆動装置から空気圧を調整することによって行う．空気圧調整は，駆動装置を病院中央配管の圧縮空気（場合によっては外部コンプレッサー）と吸引に接続することによって行うが，入院が必要となる．植込み型の特徴は電気駆動が主流で，ドライブライン（血液ポンプを駆動する信号伝達コード）のみが皮膚を貫通している．植込み型は駆動装置が小さいうえに，バッテ

リーを装着すれば外出も可能で自宅退院ができる.

C LVADの適応

開心術後重症心不全
劇症型心筋炎
慢性難治性心不全

LVADの適応病態を表2に示す. このうち, 開心術後重症心不全, 心筋梗塞合併症, 劇症型心筋炎は, 主に自己心機能の回復までの短期から中期の補助を目的としている. 心筋症などの慢性難治性心不全の増悪に対するLVAD装着は, 長期に必要なことが一般的である. 慢性難治性心不全が増悪した場合には, 自己心が回復しLVADより離脱できる場合は少なく (植込みの10～20%), 多くの症例は心臓移植の適応となる.

D LVADの合併症

合併症として, 血栓塞栓症 (脳梗塞など), 出血 (脳出血など), 感染症などがある. 東洋紡国立循環器病センター型では補助が長期に及ぶと

表2 補助人工心臓の適応病態

①開心術後体外循環離脱困難症
②開心術後低心拍出量症候群
③急性心筋梗塞またはその合併症による心原性ショック
④劇症型心筋炎による重症心不全
⑤慢性難治性重症心不全の急性増悪

<慢性難治性重症心不全患者 (5) に対する補助人工心臓 (LVAD) の適応>

- 適応病態
  内科的治療およびIABPやPCPSに反応しない心不全
- 血行動態
  (適切な治療を行っているにもかかわらず) 収縮期血圧80mmHg以下, 肺動脈楔入圧20mmHg以上, 心拍出係数2.0以下, 時間尿量0.5mL/kg以下
- 臨床経過
  急激な血行動態の悪化
  進行性の呼吸不全：人工呼吸器管理を必要とする場合
  進行性の腎機能障害：BUN 40mg/dL, Cr 2.0mg/dL以上
  進行性の肝機能障害：総ビリルビン 2.0mg/dL, GOT/GPT 200U/L以上
  多臓器不全の出現

凝固能のコントロール check!

抗凝固療法が不十分であると, 脳梗塞などの血栓塞栓症, 効きすぎると脳出血などを起こす危険性が高くなります. 体外式では皮膚を貫通するチューブが太いために貫通部からの逆行性感染には十分に注意します.

ポンプ内に血栓ができることがあるので，ワーファリン®と抗血小板剤投与を必要とする．プロトロンビン時間をPT-INR 3.0～4.0にコントロールする．

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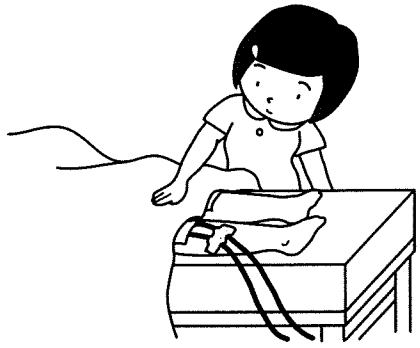
補助循環中の観察

看護のツボ



IABPやPCPS送血カニューレが挿入されていると足背動脈の拍動が触れなくなることがあります．ドプラ聴診器で聴取可能であれば通常は問題ありませんが，血流音が消失したり，チアノーゼや著明な冷感が観察されるときには，IABP抜去や位置変更が必要になることがありますので注意深く観察します．

（小野　稔）

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Original Article

Association between Gamma-Glutamyltransferase Levels and Insulin Resistance According to Alcohol Consumption and Number of Cigarettes Smoked

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Aim: Alcohol intake may increase serum gamma-glutamyltransferase (GGT) but reduce insulin resistance. We analyzed the association between GGT and a marker of insulin resistance, homeostasis model assessment for insulin resistance (HOMA-IR), according to the drinking and smoking status.
Methods: After excluding former smokers and/or former drinkers, the data of 10,482 men who underwent general health screening were analyzed.
Results: Alcohol consumption showed a graded association with GGT. In men with current alcohol consumption of ≥40 g per day, ≥20 cigarettes per day further increased GGT levels. Alcohol consumption showed a U-shaped association with HOMA-IR. In contrast, smoking 20–39 and ≥40 cigarettes per day increased HOMA-IR as compared with never smokers. An interaction between alcohol consumption and smoking was present for GGT ($p<0.001$) and HOMA-IR ($p=0.059$). GGT was not a significant negative predictive value for HOMA-IR regardless of the drinking or smoking status.
Conclusions: Although alcohol intake showed a graded association with GGT and a U-shaped association with HOMA-IR, serum GGT can be utilized as a predictor of insulin resistance in current drinkers.

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Key words; Drinking, Cigarette smoking, Epidemiology, Insulin resistance, Liver function

Introduction

Recent epidemiological studies have shown that, besides being a biomarker of alcohol intake[1-4], elevated gamma-glutamyltransferase (GGT) may be a predictor of cardiovascular events[5], stroke[6], liver cancer[7], metabolic syndrome and type 2 diabetes[8], associations that may also be present in nondrinkers[9]. Several factors other than alcohol are known to affect serum GGT levels, including coffee consumption[10, 11] and obesity[12]. In addition, a recent study has demonstrated that cigarette smoking may also increase serum GGT levels, especially in men with moderate to heavy alcohol consumption[1,3]. Furthermore, alcohol consumption may improve insulin sensitivity and lower the incidence of metabolic syndrome[14-19]; therefore, drinking may increase GGT and decrease insulin resistance. On the other hand, it has been reported that serum GGT has a positive association with insulin resistance[20, 21]. To this end, we investigated the effect of drinking and smoking on GGT and HOMA-IR values, and whether the mode of association between GGT and insulin resistance was affected by drinking and smoking in Japanese men who underwent general health screening.

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Methods

Study Population

The study was approved by the Ethics Commit-

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tee of Mitsui Memorial Hospital and the Faculty of Medicine, University of Tokyo. Between January 2004 and April 2007, 33914 individuals underwent general health screening, among which information on alcohol consumption was available in 26952. Of these 26952 individuals, information on smoking behavior was further available in 24811, of which 15183 were male individuals and were enrolled in the current study. We were unable to identify any specific reasons to explain why some subjects failed to complete the questionnaire about their smoking and drinking status. Among 15183 individuals enrolled in the current study, data on hepatitis C core antigen (HCcAg) and hepatitis B surface antigen (HBsAg) were available in 14829 individuals (98%), of which 71 were positive for HCcAg and 175 were positive for HBsAg. Individuals who were positive for either type of chronic hepatitis virus infection were significantly older (56 ± 10 years) than hepatitis-negative subjects (53 ± 10 years), although GGT levels were not different between hepatitis-positive (52 ± 52 IU/L) and -negative (58 ± 84 IU/L) individuals. We did not exclude individuals who were taking antihypertensive, antidiabetic, or antidyslipidemic drugs, which might have affected insulin resistance and serum GGT levels, from the current study population.

In Japan, regular health check-ups for employees are a legal requirement; all or most of the costs of the screening are paid for either by the employee's company (about two thirds of individuals attending our institute) or by the subject themselves (about one third of individuals attending our institute). Blood pressure was measured after about 10 min of rest by an automated sphygmomanometer. Individuals were judged to be former smokers and/or former drinkers, if they had stopped cigarette smoking and/or alcohol drinking, respectively, more than one month before their attendance.

Laboratory Analysis

Blood samples were taken from the subjects after an overnight fast. Serum levels of total cholesterol (TC), HDL-cholesterol (HDL-C), and triglycerides (TG) were determined enzymatically. Serum GGT levels were measured enzymatically. Hemoglobin A1c was determined by latex agglutination immunoassay. Plasma glucose was measured by the hexokinase method and serum insulin by enzyme immunoassay. Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated according to the following formula: HOMA-IR = [fasting immunoreactive insulin (μU/mL) × fasting plasma glucose (FPG; mg/dL)]/405.

Statistical Analysis

Data are expressed as the mean ± SD unless stated otherwise. Analyses of variance with trend analysis, Dunnett's post-hoc analysis and multiple linear regression analysis were appropriate to assess the statistical significance of differences between groups using computer software, StatView ver. 5.0 (SAS Institute, NC) and Dr. SPSS II (SPSS Inc., Chicago, IL). A value of $p < 0.05$ was significant.

Results

Baseline Characteristics

The baseline characteristics of the study subjects are described in **Table 1**. Among 15183 men, 4534 were former smokers and 416 were former drinkers. Individuals who were former smokers and/or drinkers ($n = 4701$) were significantly older than the remaining 10482 individuals.

GGT and HOMA-IR According to Smoking and Drinking Status

Current smokers who smoked 1–9, 10–19, and 20–39 cigarettes per day were significantly younger than never smokers (**Fig. 1A**). The daily amount of alcohol consumption showed a negative graded association with age. The number of cigarettes smoked showed a positive graded association with GGT (**Fig. 1B**) and, as compared with never smokers, individuals who currently smoked 1–9, 10–19, 20–39, and ≥40 cigarettes per day had significantly higher GGT levels (by Dunnett's post-hoc analysis). Similarly, the daily amount of alcohol consumption showed a graded association with GGT, and individuals who drank 1–19, 20–39, 40–59, and ≥60 g per day had significantly higher GGT levels than never drinkers (by Dunnett's post-hoc analysis). Individuals who smoked 20–39 and ≥40 cigarettes per day had significantly higher HOMA-IR than never-smokers (**Fig. 1C**). On the other hand, as compared with never drinkers, individuals who drank 1–19, 20–39, and 40–59 g alcohol per day had significantly lower HOMA-IR levels (by Dunnett's post-hoc analysis), demonstrating a U-shaped association.

GGT and HOMA-IR According to Cross Strata of Number of Cigarettes Smoked and Alcohol Consumption

In the following analysis, we analyzed the data from 10482 individuals after excluding former smokers and/or former drinkers. The mean GGT levels and HOMA-IR values according to the smoking and drinking category are shown in **Table 2**. Current

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Table 1. Baseline characteristics

Variables	Whole	Former smokers and/or drinkers [A]	Except former smokers and drinkers [B]	*p* value ([A] vs. [B])
N	15,183	4,701	10,482	
Age, years	52.9 ± 10.4	55.6 ± 9.9	51.7 ± 10.4	<0.001
Height, cm	169.6 ± 6.0	169.1 ± 5.9	169.7 ± 6.0	<0.001
Weight, kg	68.3 ± 9.5	68.5 ± 8.9	68.2 ± 9.7	0.117
Body mass index, kg/m^2	23.7 ± 2.8	23.9 ± 2.7	23.6 ± 2.9	<0.001
Systolic blood pressure, mmHg	124.7 ± 18.6	127.6 ± 18.5	123.3 ± 18.4	<0.001
Diastolic blood pressure, mmHg	79.0 ± 11.3	81.0 ± 11.0	78.2 ± 11.3	<0.001
Heart rate, bpm	63.3 ± 9.5	63.4 ± 9.6	63.2 ± 9.5	0.373
LDL-cholesterol, mg/dL	126.7 ± 30.5	127.3 ± 30.0	126.5 ± 30.8	0.112
HDL-cholesterol, mg/dL	55.3 ± 13.4	56.9 ± 13.4	54.6 ± 13.3	<0.001
Triglycerides, mg/dL	133.7 ± 94.2	129.8 ± 83.9	135.5 ± 98.4	0.001
AST, IU/L	23.8 ± 12.1	24.0 ± 10.5	23.7 ± 12.7	0.208
ALT, IU/L	27.3 ± 19.4	26.5 ± 18.8	27.6 ± 19.6	0.001
GGT, IU/L	58.2 ± 82.9	58.3 ± 67.0	58.1 ± 89.1	0.926
Fasting glucose, mg/dL	100.3 ± 20.5	101.7 ± 20.8	99.7 ± 20.4	<0.001
Hemoglobin A1c, %	5.38 ± 0.74	5.41 ± 0.72	5.36 ± 0.75	<0.001
HOMA-IR	1.69 ± 1.52	1.74 ± 1.31	1.67 ± 1.60	0.007
Antihypertensive medication, N (%)	1,909 (12.6)	831 (17.7)	1,078 (10.3)	<0.001
Antidiabetic medication, N (%)	474 (3.1)	169 (3.6)	305 (2.9)	0.026
Antidyslipidemic medication, N (%)	674 (4.4)	276 (5.9)	398 (3.8)	<0.001
Smoking and drinking status				
Never smoker				
Never drinker, N (%)	791 (14.1)	0 (0)	791 (14.3)	
Former drinker, N (%)	90 (1.6)	90 (100)	0 (0)	
Current drinker, N (%)	4,744 (84.3)	0 (0)	4,744 (85.7)	
Former smoker				
Never drinker, N (%)	263 (1.7)	263 (1.7)	0 (0)	
Former drinker, N (%)	249 (1.6)	249 (1.6)	0 (0)	
Current drinker, N (%)	4,022 (26.5)	4,022 (26.5)	0 (0)	
Current smoker				
Never drinker, N (%)	416 (8.3)	0 (0)	416 (8.4)	
Former drinker, N (%)	77 (1.5)	77 (100)	0 (0)	
Current drinker, N (%)	4,531 (90.2)	0 (0)	4,531 (91.6)	

BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; HOMA-IR, homeostasis model assessment for insulin resistance

drinking showed a graded association with GGT regardless of the smoking status. Cigarette smoking was also positively associated with GGT in some drinking categories: smoking 10–19 ($p<0.01$), 20–39 ($p<0.001$) and ≥40 ($p<0.001$) cigarettes per day was associated with greater GGT values than never smoking in individuals who drank 40–59 g/day, and smoking 20–39 ($p<0.001$) and ≥40 ($p<0.001$) cigarettes per day was associated with greater GGT values than never smoking in individuals who drank ≥60 g/day.

Individuals with alcohol consumption of 1–19, 20–39, or 40–59 g/day had lower HOMA-IR value than never drinkers, showing a U-shaped association between current drinking and HOMA-IR. This U-shaped relationship was absent or not significant in current smoking of 20–39 or ≥40 cigarettes per day (**Table 2**). Individuals who smoked 20–39 ($p<0.001$) and ≥40 ($p<0.001$) cigarettes per day had higher HOMA-IR than never smokers (**Table 2**).

Multiple Linear Regression Analysis

Next, multiple linear regression analysis using GGT and HOMA-IR as a dependent variable and age, BMI, amount of smoking, and alcohol consump-

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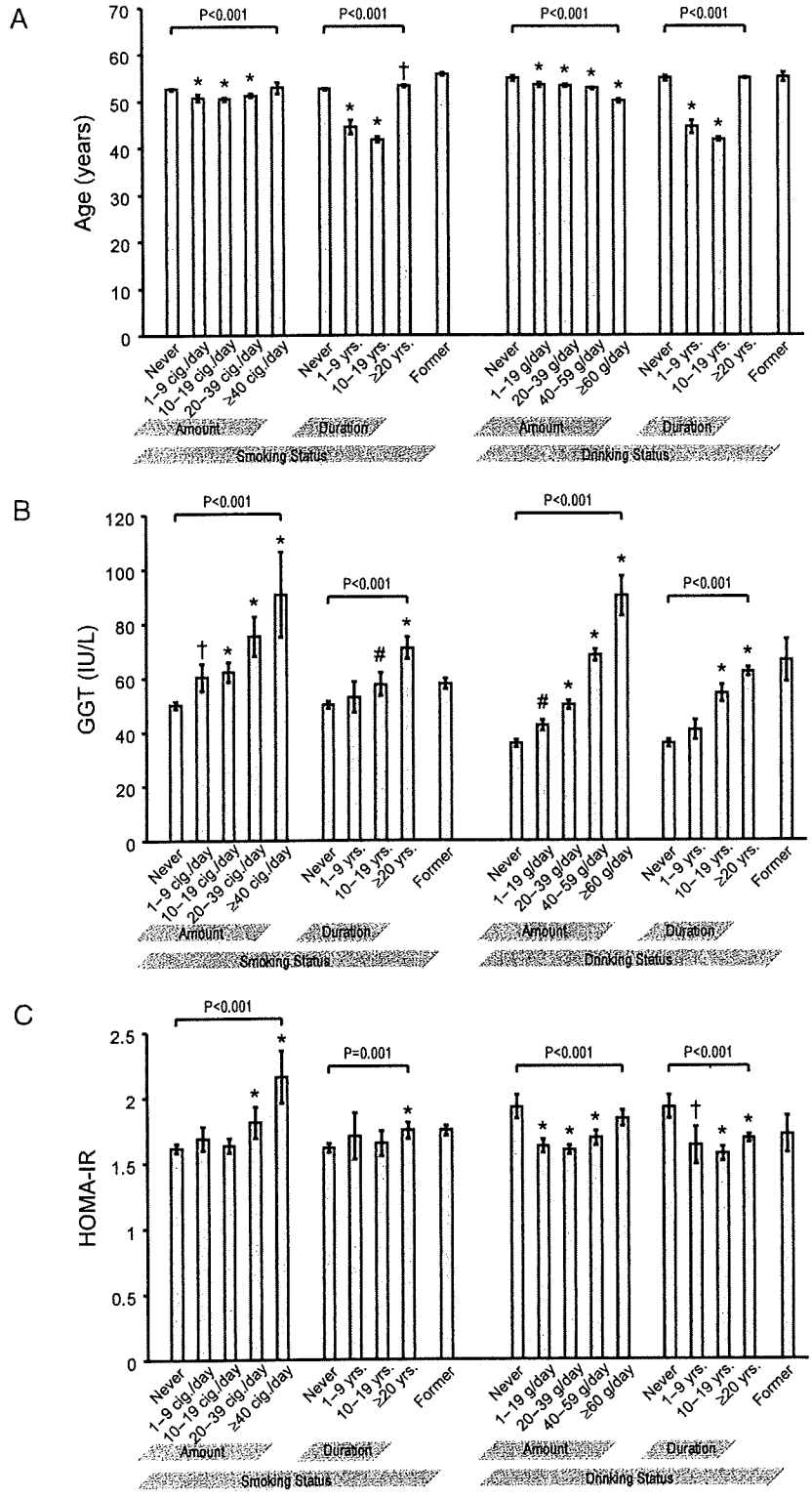

Fig. 1. Age, GGT, and HOMA-IR according to smoking and drinking status.

Bar graphs indicate the mean and 95% CI of age (A), GGT (B), and HOMA-IR. *P* values are for ANOVA trend tests. ♯, †, and * indicate $p<0.05$, $p<0.01$, and $p<0.001$, respectively, versus never smokers or never drinkers by Dunnett's post-hoc analysis.

Table 2. GGT and HOMA-IR according to smoking and drinking status

Smoking category (cig./day)	Drinking category																				
	#Overall				0 g/day (never drinker)				1-19 g/day				20-39 g/day				40-59 g/day				≥60g/day				†p value
	N	GGT			N	GGT			N	GGT			N	GGT			N	GGT			N	GGT			
		Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI		
§Overall	10,482	58.1	56.4	59.8	1,207	35.5	33.9	37.2	1,872	41.7	39.8	43.6	3,062	50.1	48.0	52.1	2,957	68.7	65.9	71.6	1,384	95.2	85.4	104.9	<0.001
									*p=	0.156			*p<	0.001			*p<	0.001			*p<	0.001			
0 (never smoker)	5,535	49.5	48.2	50.9	791	35.6	33.4	37.8	1,222	43.2	40.6	45.8	1,812	47.2	45.3	49.1	1,258	60.7	57.3	64.2	452	69.3	62.0	76.6	<0.001
									*p=	0.004			*p<	0.001			*p<	0.001			*p<	0.001			
1-9	771	59.8	54.7	64.9	48	44.0	32.4	55.6	147	39.0	33.8	44.1	207	51.1	45.4	56.8	253	69.5	57.8	81.2	116	87.1	70.3	103.9	<0.001
									*p=	0.950			*p=	0.845			*p=	0.055			*p=	0.001			
10-19	2,201	61.9	58.3	65.5	196	32.9	30.0	35.7	322	39.0	35.3	42.7	616	55.4	47.7	63.2	758	72.9	66.3	79.6	309	89.9	79.9	100.0	<0.001
									*p=	0.764			*p=	0.003			*p<	0.001			*p<	0.001			
20-39	1,748	75.6	68.1	83.0	151	35.4	32.1	38.7	158	37.0	33.1	40.9	399	55.1	50.3	59.8	623	77.0	71.4	82.6	417	122.1	93.0	151.3	<0.001
									*p=	1.000			*p=	0.413			*p=	0.010			*p<	0.001			
≥40	227	91.1	75.3	107.0	21	39.0	27.0	51.0	23	47.4	36.5	58.4	28	40.9	32.1	49.8	65	93.4	62.1	124.7	90	128.5	97.3	159.6	<0.001
									*p=	0.996			*p=	1.000			*p=	0.171			*p=	0.006			

Smoking category (cig./day)	Drinking category																				
	#Overall				0 g/day (never drinker)				1-19 g/day				20-39 g/day				40-59 g/day				≥60g/day				†p value
	N	HOMA-IR			N	HOMA-IR			N	HOMA-IR			N	HOMA-IR			N	HOMA-IR			N	HOMA-IR			
		Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI		
§Overall	10,482	1.67	1.64	1.70	1,207	1.89	1.79	1.99	1,872	1.57	1.51	1.63	3,062	1.5	1.51	1.59	2,957	1.7	1.62	1.77	1,384	1.8	1.78	1.92	<0.001
									*p<	0.001			*p<	0.001			*p=	0.001			*p=	0.878			
0 (never smoker)	5,535	1.62	1.58	1.65	791	1.83	1.70	1.96	1,222	1.58	1.50	1.66	1,812	1.54	1.49	1.59	1,258	1.57	1.51	1.64	452	1.80	1.67	1.94	<0.001
									*p<	0.001			*p<	0.001			*p<	0.001			*p=	0.995			
1-9	771	1.67	1.58	1.77	48	2.20	1.52	2.89	147	1.50	1.31	1.69	207	1.54	1.41	1.67	253	1.68	1.53	1.84	116	1.90	1.64	2.15	0.002
									*p=	0.003			*p=	0.004			*p=	0.026			*p=	0.338			
10-19	2,201	1.64	1.58	1.69	196	1.96	1.77	2.16	322	1.52	1.38	1.66	616	1.43	1.34	1.51	758	1.70	1.60	1.80	309	1.80	1.65	1.96	<0.001
									*p<	0.001			*p<	0.001			*p=	0.030			*p=	0.385			
20-39	1,748	1.82	1.70	1.94	151	2.03	1.74	2.32	158	1.49	1.31	1.66	399	1.74	1.61	1.87	623	1.92	1.62	2.22	417	1.80	1.68	1.92	0.274
≥40	227	2.17	1.97	2.37	21	1.91	1.29	2.52	23	2.71	1.98	3.45	28	1.96	1.46	2.46	65	1.84	1.52	2.16	90	2.39	2.02	2.76	0.068

†*p* values were for ANOVA trend tests. **p* values are versus never drinkers by Dunnett's post-hoc analysis. #Overall indicates all never or current drinkers, and §Overall indicates all never or current smokers. GGT, gamma-glutamyl transpeptidase; HOMA-IR, homeostasis model assessment for insulin resistance.

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Table 3. Linear regression analysis using GGT and HOMA-IR as dependent variable

	β	95%CI		Standardized β	p value
Dependent variable: GGT					
Age	−0.57	−1.82	0.68	−0.01	0.372
BMI	2.25	1.79	2.71	0.08	<0.001
Smoking	3.18	2.17	4.19	0.05	<0.001
Alcohol consumption	12.34	11.19	13.49	0.17	<0.001
Dependent variable: HOMA-IR					
Age	0.04	0.01	0.06	0.02	0.001
BMI	0.23	0.22	0.24	0.43	<0.001
Smoking	0.04	0.03	0.06	0.04	<0.001
Alcohol consumption	−0.08	−0.10	−0.06	−0.06	<0.001

For the calculation of β values, age was subdivided into 10-year increments. Alcohol consumption (g/day) corresponding to 0 (never drinker), 1–19, 20–39, 40–59, and ≥60 was coded as 0, 1, 2, 3, and 4, respectively, and smoking (cigarettes/day) corresponding to 1–9, 10–19, 20–39, and ≥40 was coded as 0, 1, 2, 3, and 4, respectively. GGT, gamma-glutamyl transpeptidase; HOMA-IR, homeostasis model assessment for insulin resistance.

tion as independent variables was performed in 10482 individuals (**Table 3**). In this model, alcohol consumption (g/day) corresponding to 0 (never drinker); 1–19, 20–39, 40–59, and 60 or more was coded as 0, 1, 2, 3, and 4, respectively, and smoking (cigarettes/day) corresponding to 1–9, 10–19, 20–39, and 40 or more were defined as 0, 1, 2, 3, and 4, respectively. Alcohol consumption was associated positively with GGT, but negatively with HOMA-IR. On the other hand, smoking was found to be associated positively with both GGT and HOMA-IR. When an interaction term between alcohol consumption and smoking was used as additional independent variable, the interaction term was found to be significantly associated with GGT ($p<0.001$), and showed a borderline significant association with HOMA-IR ($p=0.059$). The variance inflation factor (VIF) scores of all independent variables tested were less than 10 (data not shown).

Association between GGT and HOMA-IR According to Alcohol Consumption

Next, we investigated whether the mode of association between GGT and HOMA-IR differs according to the amount of alcohol consumption. For this purpose, multiple regression analysis was performed in which age, BMI, and GGT were used as independent variables and HOMA-IR was used as a dependent variable after subdividing individuals according to alcohol consumption (**Table 4**). GGT was found be a positive predictive value for HOMA-IR in 19 out of the 25 drinking × smoking categories. In some combinations of drinking and smoking, such as drinking 0 g/day and smoking 1–9 cig./day, GGT was not a statistically significant predictor of HOMA-IR. This may be in part because the number of subjects with specific drinking and smoking conditions was relatively small.

Discussion

In the current study, by analyzing the data of men who underwent general health screening, except former smokers and/or former drinkers, we observed several points: (1) Alcohol consumption showed a graded association with GGT; (2) In individuals who drank 40 g or more per day, smoking 20 cigarettes or more per day further increased GGT levels (**Table 2**); (3) alcohol consumption showed a U-shaped association with HOMA-IR, when the daily number of cigarettes smoked was less than 20 per day; (4) Individuals who smoked 20–39 and ≥40 cigarette per day had higher HOMA-IR than never smokers (**Table 2**); (5) GGT was found be a positive predictive value of HOMA-IR in 19 out of the 25 drinking × smoking categories, and GGT was not a significant negative predictor of HOMA-IR regardless of the drinking or smoking status. These data collectively indicate that, although current drinking may increase GGT and reduce insulin resistance, GGT can be utilized as a marker of insulin resistance regardless of the drinking status.

Many studies have shown that serum GGT is a biomarker of increased alcohol consumption[1-4, 22]; however, GGT is known to be affected by other con-

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Table 4. Linear regression analysis using HOMA-IR as dependent variable

		β	95%CI		Standardized β	p value
Current smoking - 0 cig./day (never smoker)						
0 g/day (never drinker)	BMI	0.20	0.16	0.24	0.33	<0.001
	GGT	0.07	0.03	0.11	0.12	0.001
1–19 g/day	BMI	0.22	0.19	0.24	0.42	<0.001
	GGT	0.04	0.02	0.05	0.12	<0.001
20–39 g/day	BMI	0.21	0.19	0.22	0.49	<0.001
	GGT	0.03	0.02	0.05	0.13	<0.001
40–59 g/day	BMI	0.18	0.16	0.20	0.47	<0.001
	GGT	0.04	0.03	0.04	0.20	<0.001
≥60 g/day	BMI	0.26	0.23	0.30	0.57	<0.001
	GGT	0.02	0.01	0.04	0.13	0.001
Current smoking - 1–9 cig./day						
0 g/day (never drinker)	BMI	0.44	0.21	0.67	0.49	<0.001
	GGT	0.13	−0.02	0.28	0.22	0.084
1–19 g/day	BMI	0.24	0.17	0.32	0.47	<0.001
	GGT	0.07	0.01	0.12	0.18	0.016
20–39 g/day	BMI	0.18	0.13	0.23	0.42	<0.001
	GGT	0.01	−0.02	0.04	0.05	0.396
40–59 g/day	BMI	0.23	0.18	0.27	0.50	<0.001
	GGT	0.01	0.00	0.03	0.11	0.049
≥60 g/day	BMI	0.27	0.20	0.34	0.57	<0.001
	GGT	0.04	0.02	0.06	0.26	<0.001
Current smoking - 10–19 cig./day						
0 g/day (never drinker)	BMI	0.16	0.10	0.22	0.34	<0.001
	GGT	0.27	0.19	0.36	0.40	<0.001
1–19 g/day	BMI	0.22	0.18	0.26	0.49	<0.001
	GGT	0.08	0.05	0.12	0.22	<0.001
20–39 g/day	BMI	0.18	0.15	0.21	0.44	<0.001
	GGT	0.00	−0.01	0.01	0.02	0.583
40–59 g/day	BMI	0.25	0.22	0.27	0.57	<0.001
	GGT	0.02	0.01	0.03	0.16	<0.001
≥60 g/day	BMI	0.22	0.18	0.26	0.54	<0.001
	GGT	0.03	0.01	0.04	0.17	<0.001
Current smoking - 20–39 cig./day						
0 g/day (never drinker)	BMI	0.27	0.18	0.37	0.42	<0.001
	GGT	0.17	0.04	0.30	0.20	0.010
1–19 g/day	BMI	0.12	0.06	0.18	0.30	<0.001
	GGT	0.07	0.00	0.14	0.16	0.036
20–39 g/day	BMI	0.22	0.18	0.26	0.47	<0.001
	GGT	0.04	0.02	0.07	0.16	<0.001
40–59 g/day	BMI	0.28	0.18	0.37	0.22	<0.001
	GGT	0.02	−0.02	0.06	0.03	0.395
≥60 g/day	BMI	0.22	0.19	0.26	0.57	<0.001
	GGT	0.01	0.00	0.01	0.15	<0.001
Current smoking - ≥40 cig./day						
0 g/day (never drinker)	BMI	−0.07	−0.29	0.16	−0.12	0.551
	GGT	0.41	0.18	0.64	0.80	0.002
1–19 g/day	BMI	−0.07	−0.29	0.16	−0.12	0.551
	GGT	0.41	0.18	0.64	0.80	0.002
20–39 g/day	BMI	0.15	0.02	0.28	0.42	0.028
	GGT	0.10	−0.15	0.34	0.17	0.425
40–59 g/day	BMI	0.18	0.06	0.30	0.37	0.003
	GGT	0.01	−0.02	0.03	0.07	0.559
≥60 g/day	BMI	0.28	0.18	0.38	0.47	<0.001
	GGT	0.05	0.03	0.07	0.42	<0.001

Standardized β values are estimates resulting from analysis performed on into standardized variables. For the calculation of β values, BMI was subdivided into 1 kg/m² increments, and GGT into 10 IU/L increments. Age, BMI, and GGT were used as independent variables. BMI, body mass index; GGT, gamma-glutamyl transpeptidase.

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ditions, such as smoking, obesity, and hepatic steatosis[23, 24]. Evidence is accumulating that higher serum GGT levels may be associated with an increased incidence of cardiovascular events[5], metabolic syndrome and diabetes[8, 25, 26]; therefore, more attention has been paid recently to this liver enzyme. It is possible that the association between GGT and various disorders observed in previous studies may be mediated, in part, by enhanced insulin resistance in subjects with increased GGT levels.

Although mild to moderate alcohol consumption may increase GGT, it may improve insulin sensitivity[18, 27], leading to a reduction in the prevalence of metabolic syndrome[17]. This finding is in contrast to the observation that cigarette smoking will not improve insulin resistance, even in light smokers[14]. As alcohol consumption has opposite effects on GGT and insulin resistance, the mode of association between GGT and HOMA-IR might differ according to the drinking status; however, only a few studies have analyzed the relationship between GGT and insulin resistance in various drinking conditions. Yokoyama and colleagues reported that GGT is associated with increased insulin resistance in non-drinkers[28] and light drinkers, but not in heavy drinkers[29], a finding that supports the notion that the mode of association between GGT and HOMA-IR differs according to the drinking status. Yamada *et al.* have reported that HOMA-IR rose with increasing serum GGT in both alcohol consumers and non-consumers, and HOMA-IR values corresponding to all serum GGT levels were lower in alcohol consumers than in non-consumers[30]. A recent study indicated that cigarette smoking may also affect both GGT and insulin resistance independent of the drinking status, and cigarette smoking and alcohol intake may have a synergistic impact on GGT[13]. Smoking status should also be considered when assessing the impact of alcohol intake on the association between GGT and insulin resistance; however, to our knowledge, no previous studies have investigated the relationship between GGT and insulin resistance after stratifying both the drinking status and smoking status, as in the current study.

We found that in 19 of the 25 subgroups divided according to smoking and drinking status, GGT was found to be a positive predictive value of HOMA-IR, which indicates that increased GGT is associated with enhanced insulin resistance regardless of the smoking and drinking status. From this type of cross-sectional study, we cannot conclude whether there is any causal or resultant relationship between GGT and HOMA-IR. A recent study showed that GGT may play a causal role in promoting insulin resistance, presumably by enhancing oxidative stress[31, 32] and hepatic steatosis[33]. Whether a change in HOMA-IR would result in a predicted change in GGT should be investigated in future longitudinal studies.

Our study has some limitations. First, we did not take into account coffee intake, which might affect GGT level[2]. Second, as the prevalence of smokers was low, we did not analyze the data of female subjects. Third, the number of daily cigarettes and alcohol consumption solely reflected the amount that was being consumed at one time, and disregarded the frequency of smoking or drinking consumption. Therefore, this estimation of smoking and drinking quantity was not equal to the mean daily number of cigarettes smoked and the amount of alcohol consumption, except in every-day smokers and drinkers, respectively. We performed such an analysis because the frequency of smoking (or drinking) was reported as a category, two or three times per week, for example; therefore, it was technically difficult to estimate the mean daily number of cigarettes smoked or the alcohol consumption. In the future, however, the frequency of drinking and smoking should also be considered in such an analysis. Fourth, we did not exclude individuals who were taking antihypertensive and/or antidiabetic drugs, which may have affected serum GGT and HOMA-IR values.

In summary, alcohol consumption showed a graded positive association with GGT and a U-shaped negative association with HOMA-IR. Cigarette smoking may further increase GGT levels in individuals who are current drinkers and drink 20 g or more per day. In 19 of the 25 drinking × smoking categories, GGT was found be a positive predictive value of HOMA-IR, and GGT was not a significant negative predictor of HOMA-IR, regardless of the drinking or smoking status. These data indicate a positive association between GGT and insulin resistance also in current drinkers.

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